

UNIVERSITÉ DE SHERBROOKE
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SUIVI DES CONCENTRATIONS DE POUDRES PHARMACEUTIQUES LORS DE LA COMPRESSION PAR SPECTROSCOPIE PROCHE INFRAROUGE ET IMAGERIE SPECTRALE

Monitoring pharmaceutical powder concentrations inside a tablet press using
near-infrared spectroscopy and spectral imaging

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To,
ANANYA, PRIYANKA, and MY PARENTS!

ABSTRACT

Pharmaceutical manufacturing has been undergoing a paradigm shift from ‘quality by testing’ to ‘quality by design’ in recent years. In the new scenario, along with a thorough understanding of product and process parameters, continuous monitoring of critical process parameters and critical quality attributes has paramount importance in order to ensure consistent product quality. Process analytical technology (PAT) tools e.g. Near-infrared spectroscopy (NIRS) are rapidly being developed for the purpose of monitoring product attributes during different stages of product manufacturing. With the advent of real-time release testing (RTRt) concept in the pharmaceutical industry, the need for monitoring all of the critical manufacturing steps is even more intensified. Consequently, there is a growing need to develop innovative and robust PAT tools for process understanding, monitoring, and control.

This Ph.D. work is directed to monitoring powder blend concentrations inside the feed frame during the tablet compression process. More specifically, near-infrared chemical imaging (NIR CI) has been introduced as a new PAT tool for feed frame monitoring comparing with NIRS as the reference method. NIR CI (‘area scan’-using discrete wavelength filter in front of NIR camera and ‘line scan’-using spectrograph in front of NIR camera) is capable of providing spectral and spatial information, both at the same time. This thesis also substantially contributes to increasing the available knowledge base on NIRS-based PAT methods for feed frame monitoring.

In the present work, the feasibility of NIR CI as a new PAT method for feed frame monitoring is verified in a 2 wheel feed frame of (Manesty Novapress) tablet compression machine both off-line and in-line. Following the optimization of sample presentation and data acquisition, the suitability of NIR CI (area scan) for feed frame concentration monitoring is evaluated in a simple composition comprising single active and 2 non-active ingredients. NIR CI is also evaluated for detecting segregation potential of the powder blends, in addition to concentration prediction (alone and in combination with NIRS). The initial off-line feasibility study led to the evaluation of in-line concentration monitoring in a pharmaceutically relevant tablet blend (single active and 5 non-active ingredients). Feed frame concentrations are compared with compressed tablets tested in-line and off-line with NIRS. Stratified tablet samples collected during the compression are also tested with ultraviolet (UV) spectroscopic

analysis for assay comparison. Finally concentration monitoring for a complex pharmaceutical blend containing 2 actives and 5 non-active ingredients) is evaluated using NIR CI (line scan) and NIRS.

NIR CI (area scan) has been found to be suitable for concentration monitoring in comparison to NIRS. NIR CI has 5x larger tested sample volume than NIRS in imaging conditions (NIR light penetration, sample area covered by NIR CI, sample density) applied in the present work. NIR CI (area scan) has been found to be suitable to detect the presence of powder blend segregation inside the feed frame. In comparatively complex pharmaceutical blend compositions, NIR CI (area scan) captures gross concentration changes as low as 2% w/w but with slightly lower signal-to-noise ratio in comparison to NIRS. Feed frame concentrations as predicted by NIRS and NIR CI closely match with compressed tablet concentrations when tested by NIRS as well as UV assay. The geometry of feed frame and placement of PAT tools inside the feed frame govern the delay in onset of concurrent concentration change in the tablets.

NIR CI (line scan) has been found successful to monitor the concentration of 2 active ingredients in a complex powder blend with a higher signal-to-noise ratio as compared to NIR CI (area scan). NIRS and NIR CI (line scan) predicted concentrations of both the actives at a similar spatial location inside the feed frame matched closely indicating similar concentration monitoring performance of these PAT tools. Capturing the entire area of the powder inside feed frame, NIR CI (line scan) gives data equivalent to multiple NIRS probes placed side by side inside the feed frame. This is certainly an advantage over NIRS since side by side placement of multiple NIR probes is not feasible considering the geometry of feed frame. Off-line calibration models have been successfully transferred to in-line monitoring; such an approach can potentially offer high material and human resource savings when monitoring newer formulations.

Overall this Ph.D. thesis successfully demonstrates the feasibility and advantages of NIR CI for feed frame monitoring in comparison to NIRS. It has the potential to become a PAT workhorse alone or along with the NIRS methods for pharmaceutical process monitoring.

Keywords: PAT; NIRS; NIR CI; RTRt; segregation; concentration monitoring; in-line; off-line

RÉSUMÉ

Ces dernières années, la fabrication des produits pharmaceutiques a connu un changement de paradigme passant de la « qualité par le contrôle » à la « qualité par la conception ». Dans le nouveau modèle de pensée, le contrôle continu des paramètres critiques de procédé et des attributs critiques de la qualité, de même que la compréhension approfondie des paramètres de produit et de procédé, revêt une importance primordiale afin d'assurer une qualité cohérente du produit pharmaceutique. Les outils de technologie analytique des procédés (PAT), par exemple la spectroscopie proche infrarouge (NIRS), se développent rapidement dans le but de surveiller les attributs qualité du produit au cours des différentes étapes de fabrication. Avec l'arrivée de concept de test de libération en temps réel (RTRt) dans l'industrie pharmaceutique, le besoin de surveiller toutes les étapes critiques de la fabrication se renforce. C'est pourquoi il est de plus en plus nécessaire de développer des outils PAT innovants et robustes pour la compréhension, le contrôle et la maîtrise des procédés.

Ce travail de doctorat vise à contrôler les concentrations de mélanges de poudre à l'intérieur de la trémie d'alimentation pendant le procédé de compression des comprimés. Plus précisément, l'imagerie chimique en proche infrarouge (NIR CI) est introduite comme un nouvel outil PAT pour le contrôle du système d'alimentation, en comparaison avec la NIRS, méthode de référence. La NIR CI est capable de fournir des informations spectrales et spatiales, et celles-ci en même temps. Cette thèse contribue également à l'augmentation considérable de la connaissance sur les méthodes PAT basées sur la NIRS pour le contrôle du système d'alimentation.

Dans ce travail, la faisabilité de la NIR CI en tant que nouvelle méthode PAT pour la surveillance du système d'alimentation est vérifiée hors-ligne et en ligne, dans une trémie d'alimentation à deux roues de la machine de compression (Manesty Novapress). Après l'optimisation de la préparation des échantillons et de l'acquisition des données, la pertinence de la NIR CI pour le contrôle de la concentration dans la trémie d'alimentation est évaluée à partir d'un mélange simple comprenant un principe actif et deux excipients inertes. La NIR CI est également évaluée pour son potentiel de détection de la ségrégation des mélanges de poudres, en plus de la prévision de la concentration (seul et en combinaison avec la NIRS). L'étude initiale de faisabilité, effectuée hors ligne, a conduit à l'évaluation du contrôle de la concentration en ligne dans un mélange approprié de comprimés pharmaceutiques (1 principe

actif et 5 excipients inertes). Les concentrations dans la trémie d'alimentation sont comparées aux comprimés testés par NIRS en ligne et hors ligne. Des échantillons de comprimés stratifiés collectés pendant la compression sont également testés par spectroscopiques UV pour la comparaison des dosages. Enfin, la surveillance de la concentration d'un mélange pharmaceutique complexe contenant 2 principes actifs et 5 excipients inertes est faite par NIR CI (balayage linéaire) et NIRS.

La NIR CI (d'image globale), en comparaison à la NIRS, est réputée adaptée au contrôle de la concentration. La NIR CI permet de tester un volume d'échantillon 5 fois supérieur à la NIRS, dans les conditions d'imagerie appliquées (entrée de lumière NIR, surface d'échantillon couverte par NIR CI, densité d'échantillon) des travaux actuels. La NIR CI est réputée appropriée pour détecter la ségrégation d'un mélange de poudres dans la trémie d'alimentation. Dans des mélanges pharmaceutiques relativement complexes, la NIR CI détecte des variations de concentrations brutes aussi faibles que 2 % w/w, mais avec un rapport signal/bruit légèrement plus faible que la NIRS. Les concentrations dans la trémie d'alimentation prédite par la NIRS et la NIR CI correspondent de près aux concentrations des comprimés lorsqu'elles sont testées par NIRS, ainsi que par dosage UV. La géométrie de la trémie d'alimentation et la mise en place d'outils PAT à l'intérieur du système d'alimentation déterminent le délai de début du changement simultané de la concentration dans les comprimés.

Le balayage linéaire NIR CI est connu pour contrôler avec succès la concentration de 2 ingrédients actifs dans un mélange de poudre complexe avec un rapport signal sur bruit plus élevé par rapport à la NIR CI à filtre unique. La NIRS et NIR CI (balayage linéaire) prévoient des concentrations des deux actifs aux emplacements spacieux similaires à l'intérieur de la trémie d'alimentation correspondent étroitement indiquant une performance de surveillance de la concentration similaire de ces outils PAT.

Capturant la totalité de la surface de la poudre dans la trémie d'alimentation, la NIR CI (balayage linéaire) fournit des données équivalentes à plusieurs sondes NIRS placées côte à côte à l'intérieur du système d'alimentation. Ceci est certainement un avantage par rapport à la NIRS, car un tel placement de sondes NIR n'est pas réalisable compte tenu de la géométrie de la trémie d'alimentation. Les modèles d'étalonnage hors ligne ont été remplacés avec succès

par des modèles en ligne ; une telle approche peut potentiellement offrir des économies importantes en matériel et en ressources humaines lors du contrôle de nouvelles formulations.

Dans l'ensemble, cette thèse de doctorat démontre avec succès la faisabilité et les avantages de la NIR CI par rapport à la NIRS pour le contrôle dans la trémie d'alimentation. Elle a le potentiel de devenir un outil PAT fiable, seul ou avec les méthodes NIRS, pour la surveillance des procédés pharmaceutiques.

Mots-clés : PAT; spectroscopie proche infrarouge (NIRS); l'imagerie chimique en proche infrarouge (NIR CI); test de libération en temps réel (RTRt); contrôler des concentrations; en ligne; hors ligne

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LEXICON

Term	Definition
Tablet	A pharmaceutical solid dosage form containing a medicament or medicaments with or without suitable excipients which is prepared by compression of the defined powder blend
Tablet press	An equipment used to make the tablets using a defined powder blend
Hopper	A piece of equipment which holds bulk powder above the tablet press and delivers it to feed frame to fill the dies
Feed Frame	Part of the tablet press that receives the powder coming from the hopper and distributes to the dies
Turret	A set of 3 concentric wheels which are used to install upper punches, dies and lower punches
Die	A cavity on die table/turret in which the powder coming from the feed frame enters to be compressed. It decides the size and shape of the tablet.
Paddle wheel	A circular wheel with peripherally attached small paddles that keeps the powder circulating inside the feed frame in order to fill into the dies
Segregation	It is the tendency of particles to separate from bulk according to their individual physical properties such as size, shape, density, etc.

LIST OF SYMBOLS

Symbol	Definition	Units
I_a	Measured intensity of reflected light	gray levels
I_b	Reflectance measured from high reflectance standard	gray level
I_s	Measured intensity of light reflected from the sample	gray level
I_b	Measured instrument response in the dark	gray level
R	Measured diffuse reflectance	gray level
\hat{y}	Predicted relative concentration	% w/w
y_0	Initial Concentration	% w/w
A	Theoretical Concentration Difference	% w/w
k	First-Order Rate Constant	% w/w per min
t	Time	min
R	NIRS Sample Area	cm ²
B	NIRS Penetration Depth	mm
C	Sample Bulk Density	g/mL

LIST OF ACRONYMS

Acronym	Definition
US FDA	United States Food and Drugs Administration
EMA	European Medicines Evaluation Agency
MHRA	Medicines and Healthcare Products Regulatory Agency
MHLW	Ministry of Health, Labour, and Welfare
WHO	World Health Organization
ICH	International Conference on Harmonization
PAT	Process Analytical Technology
CGMP	Current good manufacturing practices
CQA	Critical Quality Attributes
CPP	Critical Process Parameters
QbD	Quality by Design
NIRS	Near-infrared spectroscopy
NIR CI	Near-infrared chemical imaging
MVDA	Multivariate Data Analysis
UV	Ultra-violet
DEM	Discrete Element Method
SNV	Standard Normal Variate
MSC	Multiplicative Scatter Correction
API	Active Pharmaceutical Ingredient
PLS	Partial Least Squares
PCA	Principal Component Analysis
PCR	Principal Component Regression
FPA	Focal Plane Arrays
PCs	Principal Components
RTRt	Real Time Release Testing
AA	Ascorbic Acid
DCP	Dicalcium Phosphate Dihydrate
MCC	Microcrystalline Cellulose
R^2_{adj}	Adjusted Coefficient of Determination
RMSEC	Root Mean Square Error in Calibration
RMSECV	Root Mean Square Error in Cross-Validation
RMSEP	Root Mean Square Error in Prediction
SG	Savitzky-Golay
LIF	Light-Induced Fluorescence
RGB	Red-Green-Blue
rpm	Revolutions per Minute
RMSE	Root Mean Square Error
NIPALS	Nonlinear Iterative Partial Least Squares

CHAPTER 1 INTRODUCTION

1.1 Context and problem to solve

The availability of safe and efficacious medications is nothing less than the basic needs of all human beings. Consequently, regulatory authorities at regional, national and international levels have been established to govern the quality, safety, efficacy and availability aspects of the medicinal preparations all over the world. United States Food and Drugs Administration (US FDA), European Medicines Evaluation Agency (EMA), Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA) and Ministry of Health, Labour and Welfare (MHLW-Japan) are among the leading regulatory bodies which have pioneered the way medicinal preparations are made available to respective regional populations. In addition to these regional agencies, international bodies such as World Health Organization (WHO), International Conference on Harmonization (ICH), play a vital role in different aspects of pharmaceutical regulations related to drug product research and development, registration, manufacturing, and distribution.

The pharmaceutical industry has become highly regulated as a result of the collective efforts of these regulatory authorities. From time to time, different regulations have been enforced with the intent of having a positive impact on the quality of medications but certain numbers of associated disadvantages were also noticed over the years, e.g., as a part of regulatory framework, manufacturers are required to validate manufacturing process on 3 consecutive batches and follow the same process during routine manufacturing to ensure consistent quality of pharmaceuticals. Any change in the manufacturing process after the process validation would call for the regulatory submissions and review depending on the extent of change [1]. This being a time consuming and resource intensive process, historically pharmaceutical manufacturers had been reluctant to introduce new changes or improvements in the manufacturing process following the first regulatory approval. However, this hesitancy to introduce improvements/innovations in pharmaceutical manufacturing is undesirable for the purpose of availing safe and efficacious medications. Consequently, in order to promote voluntary innovation in product and process development, process analysis and process control; the FDA has recently undertaken different initiatives such as quality by design, process analytical technologies [2] and at the same time introduced real-time release concept

[3] to reward manufacturers for their efforts for implementing innovation in the product development and manufacturing.

The mutually beneficial nature of these regulatory initiatives has changed the mindset of pharmaceutical manufacturers which has triggered a paradigm shift in pharmaceutical research and development as well as manufacturing. One aspect manufacturing process improvement is implementing process analytical technologies (PAT) for better understanding, monitoring, and control of different stages of pharmaceutical manufacturing. Development of a PAT application for a particular manufacturing process requires through preparatory work comprising but not limited to activities such as assessing feasibility of suitable PAT tool depending upon physical nature of materials during manufacturing process, sample presentation to data collection tool, development and validation of chemometric models, analyzing results for understanding the process dynamics, etc. The context of present work lies in such preparatory work, which is aimed at developing PAT application for in-line concentration monitoring inside a tableting feed frame.

1.1.1 Pharmaceutical manufacturing regulations

Historically, the quality of pharmaceutical drug products was overseen by most of the drug regulatory authorities, including United States Food and Drug Administration (US FDA), using a two-way strategy [4]. That is: (a) assessment of the information submitted by pharmaceutical manufacturers in the drug approval application and (b) inspecting the manufacturing facility for conformance with the current good manufacturing practices (CGMPs).

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, significant opportunities now exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis and control. Unfortunately, the pharmaceutical industry has generally been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that the existing regulatory system is rigid and unfavorable to the introduction of innovative systems [2]. The industry's hesitancy to broadly embracing innovation in

pharmaceutical manufacturing is undesirable from a public health perspective. However, to exploit scientific innovations and technological advances in last few years, FDA reinforced drug approval and quality assessment process in August 2002 by launching a new initiative entitled “Pharmaceutical CGMPs for the 21st Century: science-based policies and standards in the drug regulatory approach [5].

Around the same time, the International Council on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use published series of guidelines detailing the change in the regulatory expectations for new product registration applications. ICH Q8 (R2) suggested the contents of pharmaceutical development section [3] of the product registration dossier, which is intended to provide information and understanding gained on product and its manufacturing process to the regulatory agencies. A more scientific approach to drug product development over the earlier empirical development was expected on the part of pharmaceutical manufacturers. Further emphasis on product and process understanding in terms of critical quality attributes (CQAs) and critical process parameters (CPPs) was introduced in 2007 as a part of quality by design (QbD) philosophy. A systematic approach to mitigate quality risks were outlined in quality risk management ICH Q9 [6] while effective quality management to enhance the quality and availability of medicines around the world in the interest of public health was outlined in ICH Q10 [7]. These regulatory changes throughout the product lifecycle were expected to facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

In line with QbD philosophy US FDA issued Guidance for Industry; PAT -A framework for innovative pharmaceutical development, manufacturing, and quality assurance in September 2004. In this guidance [2], process analytical technology (PAT) was put forth as a new regulatory framework to encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing and quality assurance. In November 2011, FDA announced the complete implementation of QbD starting from January 2013, expecting all companies to file new registration applications using QbD principles.

In view of increased requirements in the drug regulatory submissions, pharmaceutical manufacturing is undergoing a phenomenal change. The present work constitutes to one aspect of this change i.e. the development and implementation of PAT.

1.1.2 Process analytical technology (PAT) initiative

Pharmaceutical manufacturers are expected to demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters in the quality by design paradigm. Product and process understanding can be gained by application of, e.g., formal experimental designs, PAT, and/or prior knowledge. PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials as well as processes with the goal of ensuring final product quality [2].

In the expression ‘Process Analytical Technology’, the term ‘analytical’ is taken in the broad sense. It includes all chemical, physical and microbiological techniques as well as mathematics and risk analyses. The ideal analytical tools are those that allow for non-destructive and non-invasive real-time measurement. The FDA suggests four types of PAT tools (PAT toolbox) to measure, understand, track, and control a process. These tools are:

- Analyzers quantifying critical process parameters, i.e. spectrometers measuring the spectroscopic response of a powder blend over time to assess mixture composition change over time, e.g., time and revolutions of the blender are critical process parameters while blend concentration is a critical quality attribute for in-process powder blend.
- Statistics used in the design of experiments, i.e. factorial plans and all other techniques for evaluating as well as understanding the influence of critical parameters and their interactions with the process
- Process control, i.e. multivariate analysis and control strategies to control the process based on in-line measurements of the process parameters and product characteristics
- Knowledge management and continuous improvement, i.e. mathematical models and protocols being updated as more information is gathered during the regular manufacturing of the product.

A PAT application is defined as a combination of two or more of these tools to ensure proper monitoring and process control [2]. Such PATs can be implemented during the manufacturing operations of different dosage forms such as tablets, capsules, liquids, injectable, semisolids like creams, ointments, etc.

1.1.3 Pfizer research chair in PAT

Practical implementation of PAT tools during regular manufacturing operations requires a thorough study of all process parameters and validation of calibration models. Despite a certain number of successful PAT implementations, there is still a need for much information to be gained and exchanged between regulatory agencies as well as pharmaceutical manufacturers in the implementation of PAT assisted quality by design approach. An important reason for this is the lack of knowledge as well as practical experience in risk-based process design because industries had been using trial and error principles in the past. In this context, there is a need for collective efforts from all parties like industry, academia as well as drug regulatory bodies. As a result of such a process, Université de Sherbrooke and Pfizer have combined their efforts by creating a research chair on PAT in Pharmaceutical Engineering. This Chair has defined the following strategic objectives [8]:

- Develop knowledge on- Physicochemical phenomena governing the behavior of processes involved in the industrial pharmaceutical production (where PAT may be applied) and Criteria of “phenomenological or stochastic model-based technology transfer” (i.e. scale-up and implementation of new technologies on which PAT may be applied)
- Improve the control of processes and products based on PAT
- Consolidate the research component in the field of processes in the Department of Chemical and Biotechnological Engineering of Université de Sherbrooke and develop a critical mass of research on PAT in Pharmaceutical Engineering.

One of the ongoing projects under this research chair is to understand the powder behavior inside the feed frame using different PAT tools. Earlier work [9] used PAT tools like NIRS, RGB camera and LIF for concentration monitoring of the multivitamin product. Present work aims to broaden the earlier knowledge gained on using NIRS as process analyzer for feed frame as well as to evaluate the feasibility of new tool (Near-infrared chemical imaging-NIR CI) for the purpose of monitoring powder behavior inside the feed frame.

1.1.4 PAT in tablet manufacturing process

The tablet is one of the most common pharmaceutical dosage forms, preferred by manufacturers as well as patients. Over the years, the tablet manufacturing process has been evolved into a well-defined sequence of manufacturing operations. Tablet manufacturing is generally categorized in two ways- one based on wet granulation and another on dry granulation or direct compression. Depending upon the mode of granulation chosen, typical processes during manufacturing are weighing and dispensing, milling, sifting, mixing, granulation, drying, sizing, mixing or lubrication, compression followed by coating (film coating or sugar coating). To ensure a safety and effectiveness to the patients, a tablet formulation must deliver a constant amount of active in each dosage unit. Consequently, the powder composition of tablet formulation must be uniform in active content. However, during these dynamic operations, powder undergoes high levels of stress and strain, which can cause variable content uniformity of the active ingredients during any or all of the tableting processes.

In order to assure the quality of the blend during the tablet compression, conventionally the blend uniformity is examined at the end of final blending just before the tablet compression; additionally, the tablets are also analyzed for assay and content uniformity [10] at the end of the manufacturing process. These analyses only test the quality of the powder blend and end product. They barely help avoid adverse quality phenomena like segregation, since they don't significantly add to the product and process understanding. Furthermore, it is hard to trace quality issues back to their source if encountered at the end of such testing. In order to build a quality into the product instead of testing it, CQAs needs to be monitored during all the manufacturing operations and it can be done via the application of suitable PATs during different manufacturing operations.

Literature shows the implementation of off-line [11][12][13] as well as in-line [14][15][16] PAT for different stages of the tablet manufacturing operations for process monitoring and quality assessment. In the initial work, mostly off-line PAT developments have been reported however the advances in spectroscopic technology and availability of more adaptable process analyzers have led to the development of in-line PAT tools for continuous process monitoring. Most of the earlier work concentrated on generally regarded critical process operations of tablet manufacturing such as blending, granulation, and final product

testing for content uniformity. However, with the further understanding of the tablet manufacturing process and PAT implementation, other complex processes such as compression, coating have been evaluated by PAT implementation. In-line concentration monitoring of powder circulating inside the tablet feed frame has also been reported recently.

1.1.5 Role of feed frame in tablet compression

During the tablet manufacturing process, among all of the unit operations, consistent filling of the tablet press die with a uniform weight of powder is often both critical to quality and rate-limiting for the entire process. Uniform die filling in terms of powder weight and contents is, therefore, a crucial control variable. The amount of powder entering the die prior to compression determines the weight and overall drug content of individual tablets. Moreover, the effect of inconsistent die filling on quality is felt in less obvious ways i.e. content non-uniformity is perceived only after assaying the compressed tablets. Tablet presses use cam tracks for movement of upper and lower punches to control operations such as die fill, weight adjustment, pre-compression, compression as well as ejection of tablets. At the given settings of cam track parameters, the force at which an individual tablet is compressed depends on the amount of powder in the die [17] [18]. As a result, several final properties of the tablets including its density, porosity and the amount of elastic stress stored in the compact are affected by the amount of powder in the die.

In order to produce tablets with a uniform weight and content, there are two main requisites for a pharmaceutical powder blends. First - good flow (i.e. no bridging or rat holing in the hopper) and second - uniform content (i.e. no segregation of the active ingredient inside the hopper and feed frame). Granulation of powder blends helps to achieve good flow as well as content uniformity, however for high speed, high throughput manufacturing; this flow is not sufficient. Manufacturers often use mechanical assistance in the form of paddle feeders to maintain an adequate supply of powder to fill the dies at high speed and multiple compression stations machines

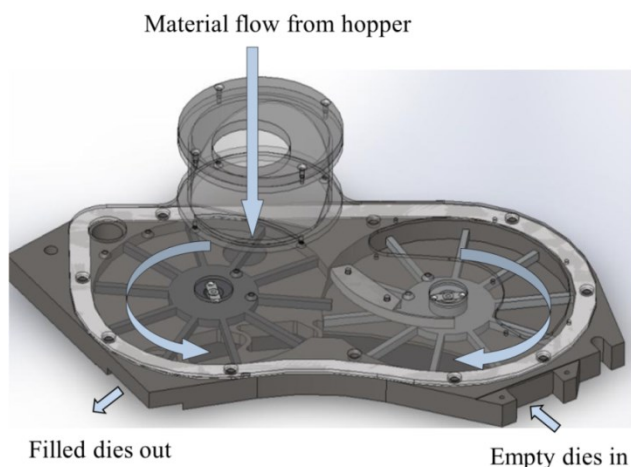


Figure 1.1 : Schematic presentation of a feed frame with 2 paddle wheel

The force feeder (referred to as feed frame henceforth) help to alleviate issues of tablet weight uniformity, however, paddles at a higher rotation speed (as shown in figure 1.1) might shear the material to a higher extent. Powder circulation at high speeds can lead to excessive lubrication and issues with a hardness of tablets. At the same time, a circulatory motion may lead to powder segregation [17][19] as the powder inside feed frame is a composite of materials having different density, particle size, shape and varied physicochemical properties.

1.2 NIR chemical imaging (NIR CI)

NIR CI is a comparatively newer technique for pharmaceutical PAT applications where sample under test is in continuous motion. NIR CI applications for process monitoring has been limited due to practical difficulties associated with accommodating the NIR chemical imaging unit on manufacturing equipment, controlling uniform and reproducible sample presentation as well as coping with time required for imaging while the sample is still moving. Conventionally NIR CI represents a distribution map of chemical/analyte obtained from NIR hyperspectral imaging, however with recent advances in technology similar sample information can be obtained with newer and faster adaptations of this methodology. Following section briefly reviews NIR CI technology and its pharmaceutical applications.

1.2.1 NIR CI acquisition

The instrumentation for acquiring hyperspectral NIR CI involves the coupling of a lens/microscope with a NIR spectrometer. There are two main types of NIR-CI systems [20] [21] :

a) Area scan imaging or staring imager system

b) Line mapping or push-broom system

Area scan imaging is considered as a real NIR CI technique when compared to line mapping system. Though the 2 techniques have different ways of data acquisition still the output result for both of these techniques is a hyperspectral data cube and the same chemical image will be obtained for a sample using the same instrument settings and data processing method.

a) Area scan imaging

The area scan imaging system does not contain any moving parts and generates images at each selected wavelength rather than collecting NIR spectra directly from the line of pixels. Area scan imaging measures the NIR absorption intensity values in each pixel of the defined sample area at one particular wavelength at a time. The imaging technique uses two-dimensional focal plane arrays (FPA), i.e. cameras having thousands of individual detector elements (pixels). The number of pixels in an image is thus fixed for area scan imaging systems and the pixel size is defined by the magnification optics (e.g. 9.8 mm/pixel magnification setting would cover 40 X 20 mm sample area using 320X256 pixels). The spectral information is obtained by changing the wavelength of light using tunable filters, e.g. liquid crystal or acoustic optical tunable filters. The NIR absorption intensity is measured in every pixel for each individual wavelength, and wavelength is sequentially changed by the tunable filter. Images at each individual wavelength are built up like a deck of cards to generate the hyperspectral data cube [20].

b) Line Mapping

The line mapping principle is based on a step-and-acquire acquisition mode. The sample area and pixel size are initially decided which fixes a number of pixels in the image. For each acquisition, diffuse reflectance spectra are collected from a line of pixels. With a very accurate positioning of a sample stage, the sample is moved and another line of spectra are obtained. In this way, a grid of spectral information is build up from all lines of spectra until spectra from all sample area are obtained to constitute the hyperspectral data cube.

In the present work, images acquired with definite bandpass wavelength filters on the NIR camera are referred as ‘area scan’ images while those acquired using spectrograph on NIR camera are referred as ‘line scan’ images.

1.2.2 NIR CI set up

During NIR CI acquisition, the sample surface is illuminated using a NIR light source and diffusely reflected light is captured using imaging optics on a focal plane array detector (Figure 1.2). Between the sample and imaging sensor, a suitable imaging optics and wavelength filter is used which helps to record images at different wavelength ranges.

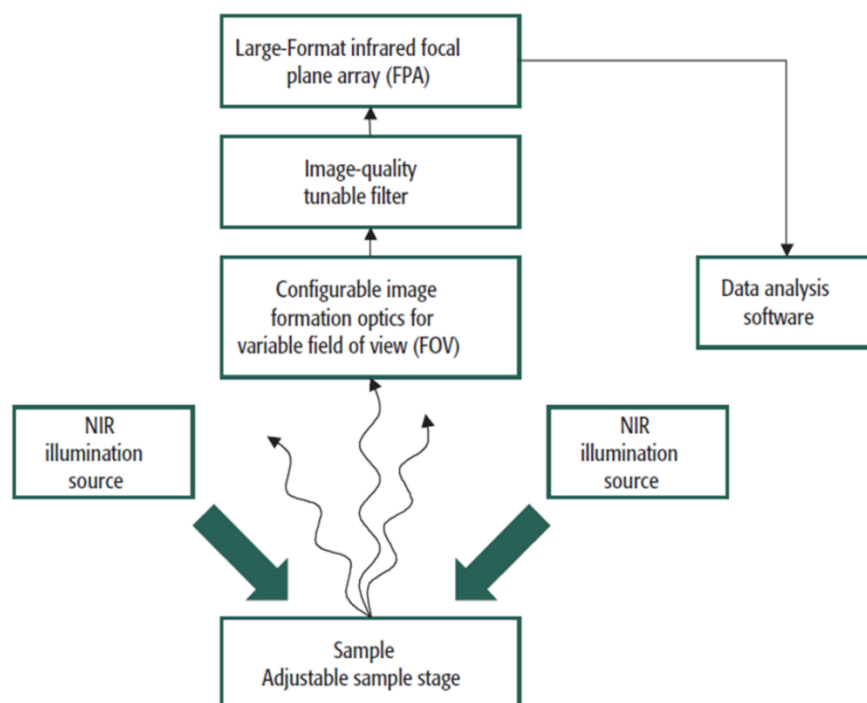


Figure 1.2 : Schematic reflection of NIR CI [22]

NIR CI gives spectral information of the sample similar to a near-infrared spectroscopy and spatial information of the sample similar to digital imaging since for a given sample NIR CI records spectral and spatial information simultaneously and provides a NIR spectrum for each pixel of the sample image. The result is a three-dimensional data set called as a hyperspectral data cube. The x, y-axis of the hyperspectral cube represents spatial information and z-axis represents wavelength. Hyperspectral data cube gives typical chemical images which provide information on the distribution of different chemical components in the sample surface. The major advantage of NIR CI over the conventional NIR spectroscopy is that it not only helps to identify and quantify surface components but it helps to know their spatial distribution from within the sample. This can be related to the quality of the product [20].

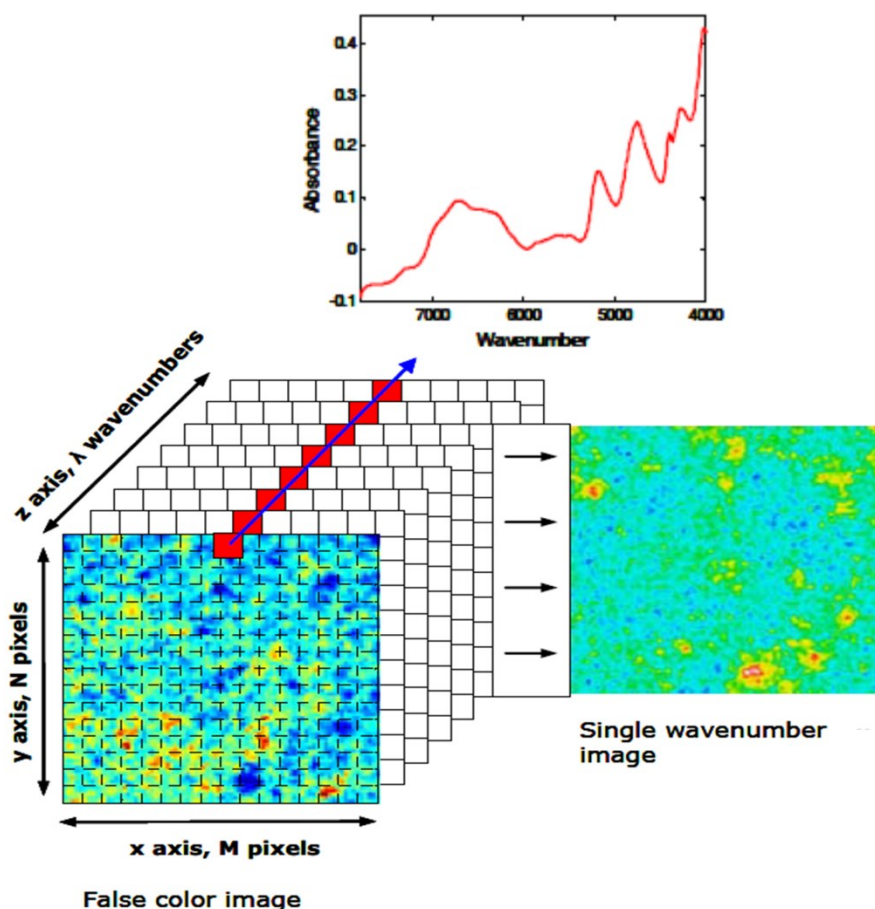


Figure 1.3 : *Schematic representation of hyperspectral NIR CI* [20]

As shown in figure 1.3, a hyperspectral data cube can either be seen as a set of array of spectra arising from every single pixel of an image or it can be seen as a set of images from which a spectrum can be generated for each pixel. Selecting a single pixel from (XY-coordinate) through the z-plane will give the spectrum recorded at this particular spatial location. This spectrum provides the spectral signature of chemical components present in that exact part of the sample. Whereas selecting one of the images from hypercube at a specific wavelength (z-value) will show the intensity values for all pixels at that wavelength. This is called a single wavelength image. The single wavelength image can be used for finding the spatial distribution of components which absorb at that particular wavelength. The hyperspectral data cube is often visualized as an image using either a grey scale or color scale to represent intensity, for example, the average absorbance intensity value for each pixel (spectrum).

In the present work, NIR CI refers to NIR images taken over a particular wavelength band using the spectral filter on the NIR camera (area scan images) or NIR images taken over 900-1700 nm range using spectrograph on the NIR camera (line scan images). NIR images taken this way do not give hyperspectral images however they offer the advantage of faster scan which is really helpful for in-line applications in testing moving material samples.

1.2.3 Spectral transformation of NIR images

There are 3 steps in the NIR CI processing:

a) *Spectral correction*

Instrument response is removed by measuring the intensity of light (I_a) diffusively reflected from of a high-reflectance standard that reflects almost 100 % light at each wavelength and instrument response (I_b) when there is no NIR light to illuminate the sample. The intensity of light reflected from the sample is then measured (I_s). The final NIR diffuse reflectance raw data (R) is calculated as the ratio between the sample and the background measurements, while instrument response in the absence of NIR light is subtracted from both of them.

$$R = \frac{(I_s - I_b)}{(I_a - I_b)} \quad (1.1)$$

b) *Conversion to absorbance*

The diffuse reflectance data (R) is organized in a three-dimensional structure (i.e. hyperspectral cube). This type of correction is also applied for NIRS data. Prior to data analysis, all raw reflectance data (R) are transformed into absorbance (A) by the relation $A = -\log_{10} R = \log_{10} (1/R)$. Assuming the path length (ι) on average is constant for the NIR diffuse reflectance mapping measurements of the sample, a linear relationship then exists between absorbance (A) and analyte concentration (c) by Beer-Lambert's law:

$$A = \text{Log}_{10} \left(\frac{1}{R} \right) = \varepsilon \times \iota \times c \quad (1.2)$$

ι Represents the path length of the sample (cm) and

ε is the molar absorptivity ($\text{L mol}^{-1} \text{ cm}^{-1}$) specific to each analyte at a specific wavenumber.

c) *Unfolding of 3D hyperspectral cube*

The three-dimensional hyperspectral data cube achieved from the NIR CI needs to be unfolded for the purpose of data analysis.

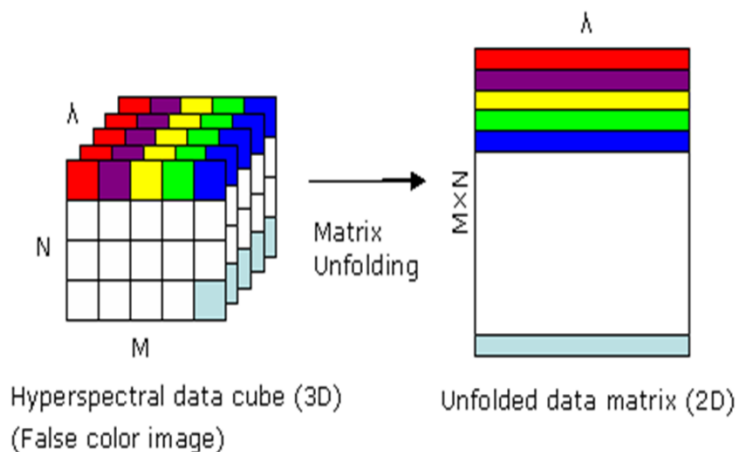


Figure 1.4: Schematic representation of unfolding hyperspectral image [20]

The hyperspectral image data is unfolded from 3D data cube to a 2D matrix (as shown in figure 1.4), in which each row is a spectrum from one of the pixels. After data processing has been done the resulting 2D matrix suitable multivariate analysis method (PCA, PLS or PCR) is selected for further analysis.

1.3 NIR spectroscopy

NIRS is one of the most frequently used techniques for sample data collection in pharmaceutical PAT applications. The suitability of a NIRS procedure is dependent upon many factors, including the instrumentation, applied chemometrics as well as the sound understanding of the physicochemical basis of the measurements [23]. The following sections contain a brief review of NIR spectroscopy basics, its use in monitoring various pharmaceutical processes as well as recent applications in the feed frame monitoring.

1.3.1 NIRS brief theoretical background

NIRS is generally chosen as the method of sample analysis because of its speed and non-destructive characteristic towards the analyzed sample. Over time, instrument improvements and the development of fiber optics have made it possible to delocalize measurements [24].

The frequency range of the NIR from 800-2500 nm mainly covers overtones and combinations of the lower-energy fundamental molecular vibrations that include at least one X–H bond vibration. Overtones (electron excitations to higher energy levels) are similar to octaves in a musical scale, like harmonics of the fundamental vibrational frequencies. Combination bands are the sum of two different vibrations corresponding to different chemical

bonds.[25] These bonds are significantly weaker in absorption compared with the fundamental vibrational bands from which they originate.

The functional groups showing NIR absorbance are mostly those involving the hydrogen atom: C–H, N–H, and O–H (Figure 1.5). Thus, NIRS represents in effect the chemical spectroscopy of the hydrogen atom in its various molecular manifestations [26]. NIR light is absorbed to different extents by the sample at frequencies similar to vibrational frequencies of the NIR active chemical bonds present in the sample.

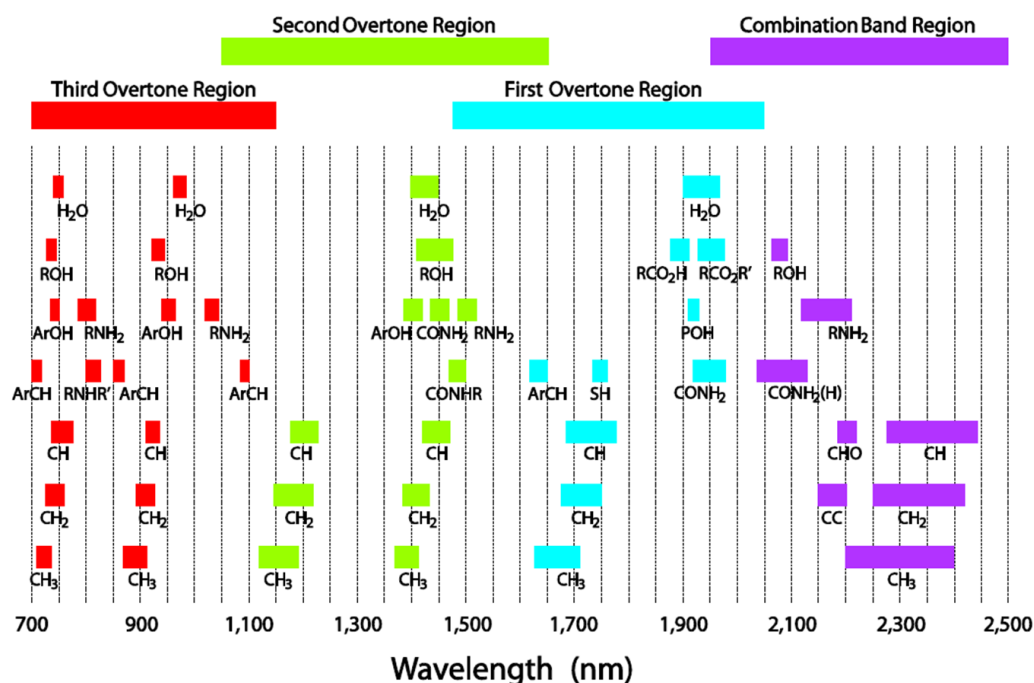


Figure 1.5: Different functional groups and their NIR absorbance range [27]

In terms of the analytical specificity, NIRS is sensitive to the frequency and intensity of these X–H NIR absorption bands and their near neighbors in the molecular structure. The local electronic environment has a particularly strong influence on the X–H bond force constants which helps to derive remarkably high information content in NIR spectra. Furthermore, some particular functional groups (e.g. O–H, N–H) are very strongly affected by both intermolecular and intramolecular H-bonding effects, with sometimes dramatically influences the intensity and band-shapes in the NIR.

In the present research work, Ibuprofen and Ascorbic acid have been used as representative pharmaceutical actives. Both these molecules show NIR absorbance owing to their chemical structure. As shown in the figure 1.6, these molecules have NIR responsive

chemical bonds in different configurations such as C–H, O–H, CH=CH, CH–CH₃, etc. (Ibuprofen) and C–H, O–H, CH=CH, etc. (Ascorbic acid). In addition, constituent excipients such as Mannitol also show NIR absorbance due to chemical bonds such as C–H, O–H.

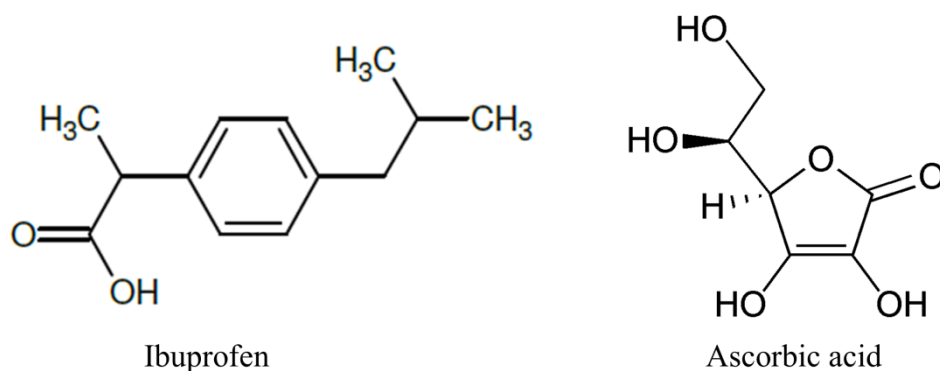


Figure 1.6: Chemical structure of Ibuprofen and Ascorbic acid [28][29]

The absorptivity of vibrational overtone and combination bands is much weaker in NIRS spectra of the condensed phase (i.e. sample in the solid or liquid state) hence physically thick samples can be measured without sample dilution or the need to resort to difficult short-path length sampling techniques. As a result, conventional sample preparation is redundant which favors the NIR PAT applications requiring direct measurement of the sample either in situ or after removal of the sample from the process [25] [26].

1.3.2 NIRS data collection and pre-treatments

NIR spectral data in PAT applications is recorded in one of the 2 modes, i.e. transmission (absorbance spectra) or reflectance mode (diffuse reflectance spectra). Although transmission mode allows probing the bulk sample in contrast to dominantly surface signal in the reflectance mode but the useful spectral range is mostly limited and spectra may contain more noise than reflectance spectra [30]. For chemometric model development, either full range of spectral analyzer or selective wavelength range region around the active ingredient peak can be used. Unnecessary too high or too low wavelength ranges may compromise model performance thus wavelength selection must be tested with respect to the performance of the model [15]. Recent study [31] reports selection of spectral wavelength representing specific bond frequency characteristic of the active molecule. It was further showed that selection of proper pre-treatments is necessary for data treatment on case by case basis.

NIR spectral baselines are mostly affected by different particle sizes, density differences, sample movement (wave behavior) in non-contact type measurements, NIR source intensity variations, etc. Most of the artifacts in the spectral data can be removed by use of suitable spectral pre-treatments [32]. Standard normal variate (SNV), Savitzky-Golay smoothing, derivatives, detrending, multiple scatter correction (MSC), centering and scaling to unit variance are some of the frequently used spectral pre-treatments (Appendix III) for NIRS data [33] obtained in pharmaceutical PAT applications. SNV helps to remove baseline differences due to changes in NIR path-length. Mathematically it is row-wise centering and scaling of NIR spectra. Derivatives (mostly first and second derivative) are used to remove peak overlap as well as to remove constant and linear baseline drifts between different spectra. Savitzky-Golay smoothing is generally used after derivatives to smoothen the spectral appearance. Detrending removes a linear or polynomial fit from the spectra to remove tilted baseline variations. MSC removes baseline offsets and multiplicative scatter effects by means of regressing sample spectra against reference spectra and then correcting the sample spectra using slope and intercept of this linear fit.

Following the spectral pre-treatments, NIR spectra are further analyzed using univariate or multivariate chemometric methods.

1.4 Definition of a current research project

As described in section 1.1.5, the feed frame plays an important role in the tablet manufacturing process since it helps in tablet weight and content uniformity as well as it is the last piece of equipment allowing access to flowing powder before compressing the tablets. At this point the tablet mass and content (potency) become fixed; thus, it is important to maintain consistent powder fill weights into the tablet dies as well as avoid any segregation of the powder blend in the process [4]. To date, a lot of attention has been paid to mixing inside the blenders [14][34][35][36][37][38][39], granulation [40][41][42][43], drying and milling process [44][45][46][47][48] during tablet manufacturing but limited studies have been directed to understand and control the powder blend behavior inside the feed frame.

Some researchers have studied [18][19][49][50][51] the impact of various feed frame parameters on the powders and subsequently compressed tablets mainly using computer-aided simulations or experimental designs, however, in-line feed frame monitoring was not

achieved. Very recently, NIRS-based PAT tools for concentration monitoring inside the feed frame have been reported. Although concentration monitoring inside the feed frame was successful, poor correlation between the NIR spectral intensity and actual tablet concentrations was seen due to the location of NIR probe, powder mass buildup inside feed frame, varying powder to probe distance [15] and speed of paddle wheels [16]. NIRS-based PATs for monitoring the powder circulation inside the tablet feed frame has been successful only in the specific experimental configurations (e.g. specific powder to probe distance, probe location, paddle speed, etc.). Furthermore, the NIR probe monitors a powder blend over a small area (e.g. $2 \times 2 \text{ mm}^2$), which may or may not appropriately represent the overall bulk powder concentration, potentially limiting the detection of segregation if present. Owing to aforesaid limitations in the available knowledge base on NIRS PAT methods for feed frame monitoring, current research project addresses the need for further studies on NIRS using contact type NIR probe with larger probe head ($15 \times 4 \text{ mm}^2$) specifically meant for feed frame monitoring methods. In addition to this, attempts have been made to find another robust tool for feed frame powder monitoring as well as detecting the presence of adverse quality phenomenon such as segregation. Consequently, the present work aims to evaluate the performances of NIR CI compared to NIRS, while consolidating knowledge on NIRS-based feed frame monitoring.

Use of NIR CI is proposed as it can prove useful for in-line feed frame monitoring due to recent developments in high-speed image acquisition capabilities while limiting the shortcomings (e.g. smaller tested sample area, baseline variations) of NIRS PAT methods. NIR camera with definite wavelength bandpass filter gives a 'area scan' image of the sample (Figure 1.7 A) where each pixel in the image represents the local composition at the specific location of the sample, e.g., a 256×320 pixel image gives sample information in the form of 81920 data points. NIR camera equipped with spectrograph acquires a 'line scan' image of a sample (Figure 1.7 B), where the 256 vertical pixels represent spectral information while the 320 horizontal pixels represent spatial information of the powder sample.

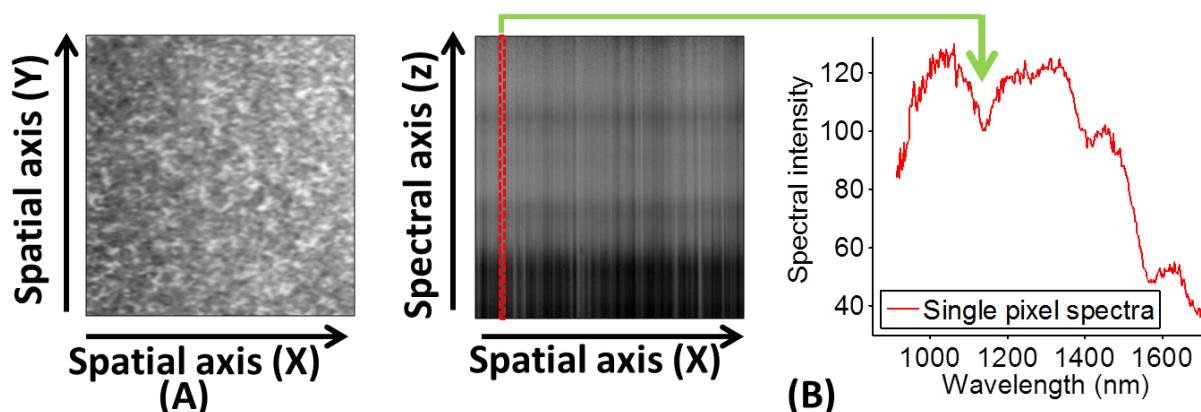


Figure 1.7: NIR CI using a single filter (A) and spectrograph (B)

Both the NIRS probe and NIR camera are placed close to each other on the second wheel of the feed frame (refer to figure 1.1) to facilitate comparison of predicted powder concentrations. The second wheel is selected for placement of these tools owing to the design of the feed frame as well as the feasibility of accommodating these tools on the tablet press (Manesty Novapress 37-station rotary tablet press).

The feasibility of using NIR CI as a process analytical tool for feed frame monitoring is evaluated using a simple blend comprising 3 ingredients while later studies are performed using pharmaceutically relevant multicomponent blends (more than 6 components) at pharmaceutically relevant concentrations. Ascorbic acid and Ibuprofen are selected as model pharmaceutical active ingredients (APIs). Feed frame monitoring is performed in two ways- a) off-line (i.e. away from compression machine) and b) in-line (i.e. at the compression machine) to evaluate the performance of selected process analytical tools as well as to transfer the calibration models to validation sets. This kind of study is important considering the possibility of making off-line calibration models using a very small quantity of the active ingredients allowing lots of saving on time and experimental resources.

NIR CI data acquisition inside the feed frame is optimized to improve signal-to-noise ratio which is later compared against the NIRS as well as tablet assay results. According to the composition of the powder blend, a suitable combination of tools e.g., NIR camera with single bandpass filter or a spectrograph is evaluated for in-line feed frame monitoring. The feasibility of NIR imaging to be used alone or in combination with NIRS, for better process understanding and control is also evaluated. NIR CI is evaluated not only for powder

concentration monitoring but also for probing the powder segregation owing to spectral and spatial information gathered from comparatively larger sample area (e.g. area scan NIR image-40×20 mm or line scan NIR image-35×3 mm) than NIRS. NIR CI (line scan) - based concentration predictions are compared with NIRS at a similar spatial location to verify comparability of these tools for feed frame concentration monitoring.

NIRS is evaluated for feed frame monitoring as well as concentration monitoring in the subsequently compressed tablets in order to verify comparison of feed frame concentration monitoring against tablet concentrations. This comparison is further tested with ultra-violet (UV) spectroscopic assay results of stratified tablet samples collected during the compression run. Powder concentration change kinetics inside the feed frame and the tablets are compared to see the average time taken to exhibit the feed frame concentration changes in tablets at given tablet compression rate and feed frame paddle speed. Such information is very useful during industrial tablet compression to avoid mixing of uniform content tablets with non-uniform tablets in the event of segregation phenomenon during the tablet compression; e.g., at the end of compression [52].

In addition to process analytical tool selection for feed frame monitoring, other parameters like sample presentation and data acquisition methods, data pre-treatment, wavelength selection, qualitative and quantitative chemometric modeling which are equally important points for the development of a suitable in-line feed frame monitoring method are studied through this project work.

1.5 The objective of the research work

The global objective of the present work is to develop a robust methodology (PAT) for monitoring powder concentrations inside the feed frame during the tableting process. My research hypothesis is: at the present state of available PAT tools for feed frame monitoring, it may be possible to introduce new tools alone or in combination with existing ones to monitor the composition of pharmaceutical powder mixtures in-line inside the feed frame during tableting process. NIR CI is selected (owing to spectral and spatial information from an increased sample area in comparison to NIRS) for evaluation as a potential PAT tool. NIRS is selected as reference method being already reported for feed frame monitoring. There are several individual objectives as listed below:

- Evaluate the feasibility of NIR CI (area scan image format) in comparison to NIRS for feed frame monitoring using simple powder blends.
- Evaluate NIR CI (based on spectral and spatial information) as a process analytical tool to gain additional process information in terms of local concentration changes and increased sample volume
- Compare NIR CI and NIRS-based concentration predictions inside the feed frame with the subsequently compressed tablet concentrations using prototype pharmaceutical composition comprising single active ingredient of interest
- Gain understanding of concentration change kinetics inside the feed frame and in subsequently compressed tablets.
- Evaluate NIR CI (line scan format) in comparison to NIRS for feed frame powder concentration predictions in a complex pharmaceutical composition involving 2 active ingredients of interest.
- Evaluate PLS calibration model transfer from laboratory to production

1.6 Original contributions

This research work has resulted in the development of additional knowledge base for the purpose of implementing NIR-based PAT tools (NIR CI and NIRS) for monitoring of powder blend concentrations inside the tablet feed frame. Original contributions of this Ph.D. thesis work have been presented in the form of 3 research articles (one published, second submitted and third in the process of submission).

Paper 1

Evaluation of NIR CI feasibility in feed frame environment and its concentration prediction performance in comparison to NIRS in the article titled- Concentration monitoring with near-infrared chemical imaging in a tableting press

Implementing NIR CI for feed frame monitoring was perceived to be a challenging task due to the continuous and wavy movement of the powder inside the feed frame as well as due to first time implementation of NIR CI in feed frame setting. Sample presentation was successfully optimized to get suitable signal-to-noise ratio in NIR CI data as well as NIR CI was found equally capable to predict powder concentrations inside the feed frame. NIR CI was reported advantageous over NIRS owing to the potential of probing local concentration

variation (i.e. segregation) inside the feed frame since NIR CI captured larger area of powder sample inside the feed frame.

Paper 2

Comparison of in-line feed frame concentration monitoring against in-line concentration monitoring of subsequently compressed tablets and chemical assays of stratified tablet samples in the article titled- NIRS In-line monitoring of Ibuprofen during and after tablet compression using Near-Infrared spectroscopy

NIRS-based in-line concentration monitoring inside feed frame and tablets (using different NIR probes) was compared using off-line NIRS and UV assay testing of stratified tablet samples. NIRS-based concentration predictions and concentration change kinetics inside the feed frame was compared with the subsequently compressed tablets. A delay in the onset of the concentration change in the tablets was seen in comparison to feed frame and it was reported due to the position of NIR probe as well as the design of feed frame. Except for the delay, concentration predictions in the feed frame as well as in tablets matched closely with UV assay of the stratified tablet samples.

Paper 3

Evaluating performance of NIR CI against NIRS for a complex blend with 2 actives and NIR responsive excipients in the article titled- Simultaneous monitoring of Ibuprofen and Ascorbic acid concentration inside the feed frame using Near-infrared imaging and spectroscopy

Following the positive outcome of initial feasibility in NIR CI implementation, more complex blend was evaluated using NIR CI in line scan format giving output similar to NIR probe. NIR CI offered an opportunity to evaluate radial segregation inside the feed frame as it sampled the powder across the width of the feed frame. In addition, PLS calibration model transfer from laboratory to production was demonstrated.

1.7 Document plan

CHAPTER 1

This chapter introduces the topic of this Ph.D. in reference to global and specific context to pharmaceutical manufacturing.

CHAPTER 2

The state of the art, which enumerates background concepts related to present work as well as summarizes earlier research work in the area of implementing PAT in pharmaceutical manufacturing with specific emphasis on tablet manufacturing and monitoring feed frame of the tablet press.

All of the research work performed under this Ph.D. project is presented in 4 different chapters.

CHAPTER 3

Evaluates the feasibility of NIR CI (single filter NIR images) in comparison to already known PAT technology (i.e. NIRS) for feed frame monitoring while using comparatively less complex blends (single active and 2 other non-active ingredients) than a typical pharmaceutical tablet composition. Initial challenges in implementing NIR CI inside the feed frame and resulting modifications in the experimental set up are discussed. In addition to successful concentration prediction, NIR CI ability to identify local concentration variations has been reported.

CHAPTER 4

Following a successful feasibility study (chapter 3), concentration monitoring of a single model drug (Ibuprofen) in a pharmaceutically relevant blend composition was evaluated, during the compression (NIR CI + NIRS inside feed frame) and after the compression (NIRS in tablets). Chapter 4 reports NIRS-based studies inside feed frame and tablets, subsequently, chapter 5 reports NIR CI-based studies inside the feed frame. Different NIR probes were used to monitor powder blends and tablets in an in-line manner. Tablet samples selected during the entire compression were also tested in an off-line manner. Concentration predictions for powder blends and tablets using NIRS PLS models were compared against the UV method assay results of stratified tablet samples taken during the compression process. This chapter not only compares different NIRS probes and sample presentations but also establishes a link

between feed frame concentration monitoring and tablet assays, showing how the feed frame powder concentrations represent assay results of subsequently compressed tablets.

CHAPTER 5

Powder concentration prediction inside the feed frame using NIR CI (by definite bandwidth filter) was found to be slightly less efficient than NIRS due to lower signal-to-noise ratio in the presence of multiple ingredients as well as lower specificity of the filters owing to broad range of wavelengths which are allowed to pass through the filter (filter width is 20-60 nm). Following these results, it was hypothesized that spectrograph based NIR images could be more precise and may lead to the higher signal-to-noise ratio.

CHAPTER 6

Having evaluated NIR CI feasibility against NIRS using simple blends (chapter 3) and later linking feed frame monitoring with tablet assays (chapter 4), chapter 6 discusses in detail about monitoring complex formulation composition containing 2 active ingredients and 5 other excipients inside the feed frame using NIR CI while keeping NIRS as a reference. NIR CI was obtained in 'line scan' format using spectrograph (instead of bandwidth filters) achieving spectral information similar to NIRS. PLS calibration model transfer from lab to production and from batch to batch has been reported. In addition to successful concentration prediction inside feed frame, NIR CI also gives the opportunity to predict concentration along the width of the feed frame giving an opportunity to verify spatial segregation phenomenon inside the feed frame.

CHAPTER 2 STATE OF THE ART

The main focus of the present Ph.D. project involves developing NIR CI-based methods for monitoring the powder concentrations inside the feed frame in comparison to NIRS. As such these tools alone do not have any utility in process monitoring, however, data generated by their implementation for process monitoring can be used to infer process status, e.g. active concentration within or out of pre-determined limits, segregation etc. Different chemometric techniques are used for the purpose of relating gathered data to the process parameter of interest. Consequently, process monitoring via PAT tools needs a proper understanding of the operating principles of the analytical tools, their suitability for gathering sample data based on chemical composition of powder samples to be monitored, spectral data acquisition, pre-treatment, and analysis as well as the design of rational experimental protocol to understand the process dynamics. This chapter reviews the earlier research work done to probe the feed frame role in tablet compression, basics of referred PAT tools i.e. NIRS and NIR CI, their applications in pharmaceutical process monitoring and different chemometric methods used for data analysis.

2.1 Criticality of feed frame operation

Conventionally, the feed frame has been added into the compression machine with the intention of beneficially impacting the tableting process; however, in reality, it can hamper the quality adversely if not operated properly, e.g., segregation inside feed frame [19][53]. Consequently understanding the functioning of the feed frame, its impact on product quality as well as continuous quality monitoring inside feed frame is necessary. However, the feed frame is not easily accessible for exploring process dynamics due to its design and location on the tablet press. As a result, researchers frequently used [19] [50] [53] computer-based simulations (e.g. DEM- discrete element modeling) to better understand the material dynamics inside the feed frame without actual experiments. One of the main phenomena known to adversely affect quality is particle size segregation inside the feed frame and during the die filling stage. In the work of Méndez et al [19], velocity profiles and particle vectors showed the percolation phenomenon as the most significant segregation mechanism. Paddle wheel speed was demonstrated to be the most important factor to control particle size segregation inside the

feed frame, underlying the importance of the feed frame speed during commercial tablet compression whereas a general practice the machine operators choose the feed frame speed to obtain uniform weight tablets.

DEM simulations performed [50] to evaluate the impact of varying particle, process, and equipment parameters on powder flow characteristics inside a single paddle wheel feed frame of a laboratory-scale tablet press showed widely varying particle flow patterns and residence time distributions at varying paddle wheel shape, rotation direction, and rotation speed. Faster paddle wheel speeds generally lead to more uniform tablet masses whereas slower paddle wheel speeds perform less work on the particles (a surrogate for attrition) and move the particles a smaller distance (a surrogate for the extent of lubrication) in the feed frame before they enter a die and are compressed into a tablet.

Simulation studies helped to forecast the potential impact of feed frame parameters on the blend flowing through it, however, in practical situations still the understanding was not so clear. In addition, diverse quality issues starting from tablet compression feasibility to content uniformity of tablets have led to seek much attention from pharmaceutical formulation researchers. As a result, cause and effect type studies analyzing the impact of different feed frame parameters on subsequently compressed tablet properties have been carried out. One such study performed by Mendez et al [18] described the powder phenomena inside the feed frame between 24-72 revolutions per minute of a paddle wheel. Within the experimental ranges studied it was found that:

- (a) The total shear applied to the powder was seen higher at lower die disk speeds and higher feed frame paddle speeds,
- (b) The die weight variability increased as the die disk speed increased at constant feed frame speed,
- (c) The average residence time decreased as the feed frame and die disk speeds increased,
- (d) The flow properties improved as a consequence of the shear applied.

Powder lubrication inside the feed frame and the subsequent effects on tablet hardness and dissolution has been studied [54]. Results show that large amounts of total shear applied reduced the dissolution rate of drugs, tablet hardness, and increased the powder flow. The shear applied inside the feed frame had a small effect on tablet hardness and dissolution results in case of non-lubricated material.

Most of the findings in feed frame based studies may and may not be generalized as material attributes (density, particle size, shape, segregation tendency, comparative proportions, etc.) are also required to be considered case by case basis. As a result, an in-line analysis (while compression is ongoing) of powder materials flowing inside the feed frame would be an ideal way of feed frame testing and it could also help to control the compression process via feedback controlled mechanism. Although initial work in this manner necessitates exhaustive time and resources, few researchers in the recent time have tried to develop NIRS-based in-line monitoring methods to understand bulk phenomenon going inside the feed frame. Relevant studies are discussed later in section 2.4.

2.2 NIRS suitability for PAT

NIRS is one of the most widely used PAT tools that has been used at various stages of process manufacturing, from raw material verification, moisture content monitoring in drying processes, and end-point monitoring in blending to active-ingredient tablet assay. Conventional NIR spectrometers are typically expensive and bulky systems designed with Czerny Turner grating-based systems or Fourier-transform technologies [26]. Fourier-transform infrared technologies, in particular, require high precision and costly mechanical components. However, in recent times, technological advances have led to the development of cost-effective and easy to use a type of NIR spectrophotometers. The design of these spectrophotometers is such that they can be used for online analysis of many processes of pharmaceutical manufacturing. Smaller sizes, reduced scan times, adaptability to wireless data transfer, the possibility of using at the exact location on a running machine, easy calibration and operation are certain favorable points for the rapid rise in NIR probe type spectrometers use in pharmaceutical industry.

Advanced designs of the light source, filters, optics, and detectors have helped to reduce the size of spectrophotometers. A detailed description of NIR probe technology is presented in Appendix I.

2.3 Pharmaceutical PAT applications of NIRS

There are multiple possibilities to use NIR spectroscopy at different manufacturing operations for the purpose of in-process quality control as well as final product testing. The most common application of NIR spectroscopy in pharmaceutical manufacturing operations is

concentration monitoring of active pharmaceutical ingredients. Literature search suggests use of NIR spectroscopy in monitoring the API concentration during the blending operation [34] [35] [36] [37], granulation [40], flow in hoppers or inside blender [13] [55], as well as assessing tablet uniformity, hardness, coating thickness and dissolution [56] [57]. Sample presentation to NIR probe/spectrophotometer is a most critical aspect to obtain the reproducible results. All of the aforesaid applications mostly tested the sample in the form of steady surface and thus reproducible and uniform NIR spectra were obtained for every sample. On the contrary, dynamic process samples like in the case of feed frame, NIR spectra measurement is more challenging. However, as mentioned earlier, advances in detectors, light sources and filters have to lead to flexibility in developing NIR applications for dynamic pharmaceutical manufacturing processes. As a result, NIR spectroscopy has been explored recently as a PAT tool in the monitoring of pharmaceutical powders on-line in feed frame, immediately before compression into tablets.

NIR, with its unique features like high-speed sampling and rapid spectral acquisition, can be used to assess distribution of individual blend components with high accuracy during blending. NIR analysis can be beneficial on many aspects of pharmaceutical blendings, such as: (a) Real-time quality monitoring; (b) Improved process efficiency as well as a performance by selecting adequate process parameters e.g. blending time; (c) Quality by design initiatives during the development of blending processes for new formulations.

PLS calibration models spanning the wide concentration range of blend components have provided accurate and robust concentration predictions in blending operations [37][36].

Along with concentration predictions, NIR spectroscopy applications have been developed to monitor the content uniformity of low dose dry powder blends and to provide an insight into the fundamental mechanisms of dry powder blending and segregation. The rotational speed of the blender has been found to greatly affect the blending and segregation. Some speeds promote segregation while others promote mixing or change the mode of segregation. Axial segregation was promoted by the blender speeds which promoted the difference between the 'angle of repose' of the two powders [34].

NIR-spectroscopy based applications were used for the real-time monitoring of critical parameters during the continuous wet agglomeration. In a continuous wet granulation process, the solid-state characteristics and particle size of the granules were analyzed in real-time and

the critical process parameters influencing these granule characteristics were identified [40]. The temperature of the granulator barrel, the amount of granulation liquid added and, to a lesser extent, the powder feed rate were the parameters influencing the solid state of the active pharmaceutical ingredient (API). NIR probe was inserted inside a cuvet to make reproducible measurements.

NIR spectroscopy tools can also be used in analyzing and predicting powders flow parameters such as angle of repose, compressibility index (Carr's index) and Hausner ratio. Correlation between the reference method values indicating powder flow characteristics and the near-infrared spectrum was performed by partial least squares (PLS) for pharmaceutical blended powders consisting of paracetamol [13]. NIR-based in-line powder flow characterization in pharmaceutical formulations is also reported [57]. Application of NIR spectroscopy based models at multiple stages during tablet manufacture is possible, e.g. blend homogeneity, content uniformity of tablets as well as tablets coating thickness [58]. Along with chemical analysis, physical parameters such as tablet hardness has been reported [56]. Performance of the chemometric models was improved by spectral pre-processing.

An in-line NIRS method for determining the drug content of powder mixtures and tablets during a continuous tableting process have been reported [59]. It must be noted that the quantitative in-line monitoring of pharmaceutical products using NIR spectroscopy may be particularly problematic because the spectra of drugs and excipients are themselves complicated, and the pharmaceutical processes may further complicate the NIR spectra of production samples. However, the most recent generations of NIR instrumentation are expected to simplify both qualitative and quantitative applications and thus further enhance the utility of NIR spectroscopy for use in monitoring the challenging pharmaceutical processes. Recent advances in technology like in tunable wavelength filters, detectors, etc. have made it possible to make miniature NIR spectrophotometers that are fit to use in-line and on-line applications in continuous pharmaceutical manufacturing processes.

2.4 NIRS PAT applications for feed frame monitoring

Studying the tablet compression process has great significance in the pharmaceutical industry since most of the drugs are available in the tablet dosage form. Feed frame of the tablet press is used to fill powder into the empty dies during the tablet compression. Die

filling is one of the key steps to control final tablet properties such as weight, hardness and content uniformity. Powder flowing through feed frame is subjected to centrifugal motion, shear and compressive stress due to the motion of feed frame wheels. Thus, resulting turbulent movement of the material can lead to segregation of powders inside the feed frame which means that irrespective of powder content uniformity until hopper, eventually there may be content uniformity issues in the final tablets. In this reference, understanding, monitoring and controlling powder flow inside the feed frame is of most importance to tablet manufacturing process.

In order to understand and monitor the die filling process via in-line NIR measurements, analysis of different factors that could affect the NIR spectra acquisition is important. The spectral baselines are mainly affected by mass hold-up inside the feed frame and different paddle wheel speeds [15]. Peaks and troughs in the powder mass formed by the action of the paddles are observed inside the feed frame. In non-contact type spectral measurements, the distance from the powder bed to the NIR probe decreases with increasing paddle wheel speed leading to changes in spectral baseline variations. A difference in the average predicted concentration was observed due to changes in powder dynamics at different paddle wheel speeds. A change in powder agitation also provokes differences in powder bed density affecting the concentration prediction.

As a result of powder movement inside the feed frame, variations in the physical properties of the powder blends is pronounced. In order to develop the NIR-based feed frame monitoring approach as a robust application, sample presentation is a critical aspect that needs to be examined and controlled. Studies conducted [60] using specially designed experimental set ups to provide fundamental understanding on sample presentation, showed that with the optimized probe distance, suitable spectral preprocessing and averaging, the spectral artifacts caused by the moving dynamics can be significantly reduced.

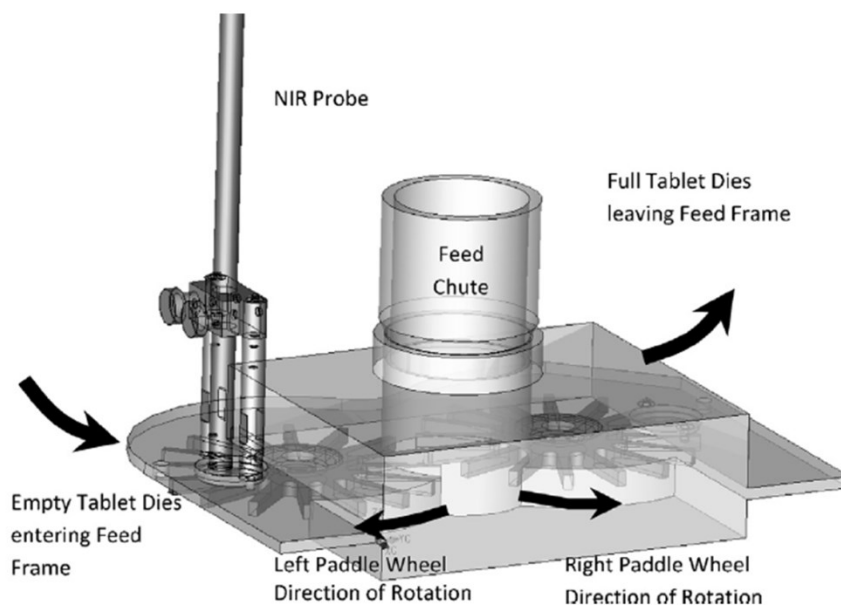


Figure 2.1: Experimental NIR set up at feed frame [16]

Stepwise understanding and subsequent improvement in the spectral data acquisition techniques have shown positive outcomes e.g. NIR spectrometer mounted on the feed frame [61] acquired high-quality NIR spectra despite being obtained from the fast-moving blend. As shown in figure 2.1, the NIR probe was installed into the feed frame showed excellent correlations between the NIR signal and weight corrected tablet potency from stratified tablet samples (4 samples within 1st min, 3 samples in 2nd min, 1 sample at each min until 10 min of tablet compression) collected over time [16]. A similar correlation was also found at higher feed frame paddle wheel speeds, however for lower feed frame paddle wheel speed a bias between weight corrected tablet potency and the NIR signal was observed; suggesting need to optimize certain process parameters such as paddle wheel rotational speed and NIR probe location for different tablet press geometries to ensure that the NIR process spectra can be related to tablet potency. Other parameters such as particle size differences in the active and excipients, differences in relative humidity and paddle speed have been reported [31] as potential variables to be considered in off-line PLS calibration model development for monitoring the continuous manufacturing operation at tablet feed frame. Application of NIR spectroscopy in the monitoring of active concentration inside feed frame is still an emerging application. Constant circulatory motion and the oscillatory sample presentation to the NIR probe appear to be a major hurdle in addition to NIR probe on the feed frame. In order

to have a better understanding of feed frame dynamics, more studies are still required to be performed, both in academic as well as the industrial setting.

2.5 Pharmaceutical PAT applications of NIR CI

NIR CI is a comparatively new PAT tool being used for pharmaceutical manufacturing applications when compared to the NIRS using probes. The major advantage of NIR CI is its capability to give both spatial and spectral information of the sample under test. Visualizing the distribution of the physical or chemical property in the sample is valuable for in-process and final product understanding during formulation development and also for troubleshooting quality defects⁵².

Quality defects in medicines are not acceptable as they can prove life threatening at the same time the cost of drug recall as a result of quality defects is very high; e.g. Drug product recalls due to sub-potent or super potent strength compared to the labeled strength is classified as class I recall. Such recalls are potentially life threatening and could cause a serious risk to health when drug contained in the dosage form is potent [62]. In the context of drug product's quality, conventional single point NIRS has been successful for estimating the global content of the physical or chemical property [63] however, spatial segregation that may lead to content uniformity issues in the dosage forms such as tablets may not be well detected

NIR CI PAT implementation in pharmaceutical manufacturing is still in the development phase but the number of its applications and chemometric methods to analyze NIR CI are increasing recently. NIR CI-based methods has been used in the determination of end point of the mixing in blender [64] [65][66][38][67][68], where notable advantage of NIR CI over NIRS is to have more statistical confidence in the end point determination since it provides information from a large area of the sample. In addition, NIR CI applications has also been used to determine tablet uniformity [69], process related troubleshooting [70], distribution map in tablet [71][72][73] blending simulations for early phase development, quantification and distribution of pharmaceutical major and minor ingredients in tablets [74]. Some novel applications like the study of polymer film formulations [75], quantification of polymorphic forms [76], water content analysis in continuous freeze drying process [77], assay of roller compacted ribbons and subsequent tablet formulations [78] have also been reported using the NIR CI.

2.6 Chemometrics in NIRS and NIR CI-based PAT applications

Chemometrics is a branch of science that derives data by the application of mathematical and statistical methods, for the extraction of useful information from physical and chemical phenomena involved in a manufacturing process [79].

Chemometrics is used for multivariate data collection and analysis, calibration, process modeling, pattern recognition and classification, signal correction and compression, and statistical process control. Both predictive and descriptive analysis may be handled by chemometrics. The predictive analysis includes numerous system properties that are used in a model with the intent of predicting the target properties, desired features, or behavior of interest. The descriptive issues include properties of the investigated systems that are modeled in order to learn the underlying relationships and the system structure, which leads to the model identification, composition, and understanding.

Chemometric methods employed for analysis of NIRS and NIR CI derived data are categorized as univariate methods and multivariate methods

2.6.1 Univariate methods

For univariate analysis, a 2-D image plane from the hyperspectral data cube or a spectral intensity at a particular wavelength in a NIR spectrum is selected. This method is useful when NIR images at specific absorbance intensities or spectral data at the specific wavelength are available. It is the easiest and fastest way to analyze hyperspectral image or NIR spectral data. However, it is necessary for the analyte of interest to have a specific absorption band in the NIR region and it is not interfered by the other components of the blend. Univariate profile of API spectral intensity at a single wavelength as a function of its concentration has been reported [61]. However, this is not always the case since pharmaceutical samples are more complex. Most of the times though active have a specific absorption band but the excipients in the blend had more broad bands that overlap with the active. As a result univariate methods are not much use in NIRS and NIR CI-based PAT applications, instead, multivariate methods are mostly used.

2.6.2 Multivariate methods

The drawbacks of univariate methods such as background variation and other interferences could be overcome by multivariate techniques. The advantage of multivariate analysis is that the entire spectrum can be used and interferences can be separated from the information of interest. There are multiple multivariate analysis methods available, however, only the methods used in the present work are discussed shortly in the following paragraphs.

a) Principal component analysis (PCA)

PCA seeks to extract the major systematic variation in a data matrix. It reduces a large dataset containing an important number of variables to only a few, called principal components (or PCs). The principal components are new uncorrelated linear combinations of the original variables. The first principal component (PC1) describes the largest variation in the data set, the second PC the second largest variation and so forth. A loading is produced for each PC. Loadings provide information about the relation between the original variables and the PCs. The loadings look similar to original spectral features and most of the times are similar to the pure spectrum of a compound if a principal component mainly explains the variation for this pure compound. Using a score value a score images for each PC are produced as the final result from a PCA analysis.

The 2 limitations seen in PCA on NIR-CI data are that a principal component score image cannot be unambiguously assigned to a specific active ingredient because it is difficult to associate the loadings with the pure compound spectra and numbers of PCs are often not in accordance with the number of chemical compounds in the sample.

b) Partial Least Squares (PLS)

PLS is a regression method that is used to relate two data matrices X (spectra) and Y (reference values). PLS need a calibration data in a range of concentrations in order to predict concentration of the unknown using the PLS model. In a PLS model, only components that are used in the calibration model are modeled.

In the PLS model building another major requirement is to get the most accurate Y matrix (reference values). Theoretical concentrations used as reference values may not take into account practical changes or process related variation in concentrations from batch to batch.

PLS models are characterized based on values of different parameters related to model fit and errors in concentration predictions as described below.

a) *Root Mean Square Error of Calibration (RMSEC)* [33]

This model parameter measures the average difference between predicted and measured response values at the calibration stage;

$$RMSEC = \sqrt{\sum_{i=1}^N \frac{(\hat{y}_i - y_i)^2}{N}} \quad (2.1)$$

where \hat{y}_i represent model predicted values of i^{th} dependent variable and y represent expected values of dependent variable in the calibration data set, N is total number of samples.

b) *Root Mean Square Error Prediction (RMSEP)*[33]

RMSEP measures the average difference between predicted and measured response values at the validation stage;

$$RMSEP = \sqrt{\sum_{i=1}^N \frac{(\hat{y}_i - y_i)^2}{N}} \quad (2.2)$$

c) *Root Mean Square Error Cross Validation (RMSECV)* [33]

RMSECV measures the average difference between predicted and measured response values of samples from the calibration set that were placed aside;

$$RMSECV = \sqrt{\sum_{i=1}^N \frac{(\hat{y}_{CV,i} - y_i)^2}{N}} \quad (2.3)$$

where $\hat{y}_{CV,i}$ represents model predicted values while y_i represents expected concentration for i^{th} sample.

d) *Hotelling's distance (T^2)*

T^2 is a non-euclidean distance of each sample in relation to the average of all samples. If a predicted concentration value of a sample is beyond the 95% limit, it indicates that the sample is different from the others, but it does not necessarily mean that it is not part of the model.

$$T_i^2 = (x_i - \bar{x})S_x^{-1}(x_i - \bar{x})^T \quad (2.4)$$

where S^{-1} is the inverse of the variance-covariance matrix of X ; x_i is i^{th} sample and \bar{x} sample group mean.

e) $Q - Residuals (Q)$

Q is off the plane distance of samples relative to the plane formed. Most of the time, samples whose distance is beyond the 95% limit, may represent an outlier of data, that is, a sample that is not part of the model and should be ignored while model building/validation. However, its interpretation must be carefully made as it might represent an unpredictable behavior of the system. Q residual is calculated as squared predicted error (SPE) [80].

$$SPE (Q) = \sum_{j=1}^i (x_{ij} - \hat{x}_{ij})^2 \quad (2.5)$$

where x_{ij} is an element of X and \hat{x}_{ij} is an element of \hat{X} (model predicted)

f) R^2 - Coefficient of Determination

R^2 is PLS model fit value which represents how well the model fits to calibration data set.

$$R^2 = 1 - \frac{SSE}{SST} \quad (2.5)$$

$$SSE = \sum_{i=1}^N (y_i - \hat{y}_i)^2 \quad (2.6)$$

$$SST = \sum_{i=1}^N (y_i - \bar{y})^2 \quad (2.7)$$

Where SSE is sum squares explained, SST is sum square total, \bar{y} is mean of all expected concentrations.

R^2 is calculated according to a number of latent variables selected in the model, in such cases R^2 is called as an adjusted R^2 square (R_{adj}^2).

$$R_{adj}^2 = 1 - \left\{ \frac{SSE}{N-k-1} \right\} / \left\{ \frac{SST}{N-1} \right\} \quad (2.8)$$

where k is number of latent variables selected in the PLS model.

Following tables summarize few representative NIRS (table 2.1) and NIR CI (table 2.2) applications in pharmaceutical tablet manufacturing operations and different chemometric techniques used therein.

Table 2.1 : Representative applications of NIRS-based Chemometric techniques during tablet manufacturing process

Application in respective tablet manufacturing operation	Chemometric method	Conclusion(s)	Reference number
a) Blending			
Monitoring of powder blending operation using multi-point NIRS measurements	PLS	Powder loading order, as well as fill level, resulted in varying blending dynamics in different zones where convective and diffusive mixing effects dominate	[81]
On-line monitoring of powder blend homogeneity by NIRS in V blender	Spectral STD	Calculation of moving block spectral standard deviation (STD) successfully determined the end point of the powder blending	[82]
Development of NIR-based blend uniformity method for multiple structurally similar actives	PCA, PLS	PCA/PLS score patterns can be used not only for selecting model parameters but also for the interpretation of models. NIR method shows satisfactory specificity and accuracy for all active concentrations	[83]
Evaluating the influence of mass flow and rotation speed in blending using NIRS	PLS	Flow and stirring rate variations caused different powder flow dynamics, which were reflected on the NIR measurements and PLS	[84]
Blend uniformity end-point determination using near-infrared spectroscopy and multivariate calibration	PLS	NIRS-based PLS method predicted blending end point successively over 3 years and was verified against HPLC assay of the blend as well as tablet samples	[85]
b) Granulation			
Real-time assessment of granule and tablet properties using in-line data from a high-shear granulation process	PLS	Compared to process data such as power consumption and temperature, NIRS spectral data correlated better to granule and tablet properties.	[86]

Application in respective tablet manufacturing operation	Chemometric method	Conclusion(s)	Reference number
Real-time monitoring of granule properties during high shear wet granulation	PCA, PLS	Granule properties can be correlated with the granulation process at the same time end point can be determined using NIRS data	[87]
c) Drying and milling			
Monitoring granulation drying using NIRS	PLS	Special NIR probe can help to reduce variations due to density change while inferring about the moisture content of granules	[88]
In-line real-time NIR granule moisture measurements of a continuous granulation–drying–milling process	PLS	NIR spectra show changes in granule moisture as the drying progresses as well as it also helps to understand the role of inlet air temperature on the total moisture content of the granules	[89]
d) Tablet assay/uniformity			
The concentration profile of active and excipient in a tablet by NIR CI	SMCR*	NIR CI can not only predict concentration but show distribution and crystal structure change of API in sustained release waxy matrix	[90]
Quantification of meloxicam and excipients in intact tablets by NIRS	PLS	NIRS PLS predicted concentrations of tablet ingredients matched closely with the HPLC-based assay of the respective ingredients	[91]
Theoretical analysis of tablet hardness prediction using NIRS	PCR	The regression factors contain both chemical and physical information enabling hardness and porosity predictions	[92]
e) Coating			
In-line NIR spectroscopy application for the monitoring of tablet film coating in an industrial scale process	PCA, PLS	Factors such as temperature, moisture, coating growth, change of tablet bed density have an impact on NIR spectra which allowed successful monitoring of tablet coating process	[93]

Application in respective tablet manufacturing operation	Chemometric method	Conclusion(s)	Reference number
Applicability of NIRS for monitoring film coating and curing process of the prolonged release coated pellets	PLS	NIRS is useful in curing monitoring as well as to predict drug release from the pellets but owing to its higher sensitivity to moisture, results were not accurate for pellets with a higher moisture content	[94]
Effect of sampling frequency for real-time tablet coating monitoring using near-infrared spectroscopy	PLS	Predicted moisture and coating level predictions from the spectral data model depend on the frequency of NIR testing in the in-line tablet coating process	[95]

* *SMCR-self modeling curve resolution*

Table 2.2: Representative applications of NIR CI-based Chemometric techniques during tablet manufacturing process

Application in respective tablet manufacturing operation	Chemometric method	Conclusion(s)	Reference number
a) Blending			
Assessment of powder blend uniformity: Comparison of real-time NIR blend monitoring with stratified sampling in combination with HPLC and at-line NIR CI	PLS	Blending end point suggested by NIRS-based blend monitoring matched with end points determination by NIR CI and HPLC analysis of stratified blend samples	[96]
Critical evaluation of methods for end-point determination in pharmaceutical blending	PLS	Powder blend homogeneity as predicted by NIRS and NIR CI was similar giving similar values of time required for blending end point	[97]
b) Granulation			
Visualization and understanding of the granulation liquid mixing and distribution during continuous granulation using NIR CI	Univariate linear regression	Increased screw speed and lower moisture content resulted in a narrower residence time distribution. Increased moisture content and higher kneading results in uniform distribution of granulation liquid.	[98]

Application in respective tablet manufacturing operation	Chemometric method	Conclusion(s)	Reference number
Linking granulation performance to residence time and granulation liquid distribution	PLS	NIR CI successfully shows moisture distribution in the granules helping to understand solid-liquid mixing during the granulation process	[99]
c) Tablet assay/uniformity			
Continuous monitoring of API content, API distribution and crushing strength after tableting via NIR CI	SD*, PLS models	NIR CI helps to gather data allowing intra and inter tablet variation of drug distribution and hardness as compared to single point NIRS testing	[100]
Quantitative testing and distribution homogeneity assessment in pharmaceutical formulations using NIR CI	PLS	NIR CI data not only helps to find API distribution but also helps in quantitative concentration prediction	[101]
Comparison of marketed tablet dosage forms for content uniformity using NIR CI	MCR*	NIR CI helps to find active distribution map for tablets manufactured by different manufacturers as well helps to decide content uniformity	[102]
A Quantitative Method using NIR CI to determine the surface composition of tablets	PLS	Averaging predicted concentration in all image pixels gives tablet API content at the same distribution maps assesses the homogeneity	[103]
d) Coating			
Quantification of components in coated pharmaceutical tablets using NIR CI	CLS*	The coating applied on the tablet represents about 30 % mass fraction of the sampled tablet which interfered in the estimation of tablet assay.	[104]

*SD- standard deviation, CLS- classical least squares, MCR: Multivariate curve resolution

CHAPTER 3 Concentration monitoring with NIR CI (area scan) in a tableting press

Title in French:

Suivi de concentration par imagerie NIR (global) dans une presse à comprimés

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Summary

Content:

In order to evaluate the feasibility and suitability of NIR CI (area scan) for feed frame monitoring, it is necessary to verify its performance against known PAT methods of feed frame monitoring. In the present work, NIR CI (area scan) is evaluated for detecting Ascorbic Acid (model API) concentrations qualitatively and quantitatively in a comparatively simple blend comprising only 3 ingredients, while NIRS is used as reference method. Additional aspects for NIR CI (area scan) such as data acquisition, tested sample volume and the possibility to find local concentration changes are also explored.

Results:

NIR CI (area scan) implementation inside feed frame is found feasible at the end of the study. NIR CI (area scan) performed closely to NIRS for concentration differentiation qualitatively as well as quantitatively. In addition to increased tested sample volume, it also shows the possibility to explore local concentration variations; in these aspects, (i.e. sample volume and segregation testing) NIR CI (area scan) appeared promising over NIRS.

Contributions to the thesis:

Current experimental work helped to present proof of concept for implementing NIR CI (area scan) for monitoring the feed frame. The initial challenges in NIR CI (area scan) implementation such as controlling sample presentation and data acquisition were successfully addressed. Concentration monitoring in off-line tests using comparatively simple blends was successful, which open the doors to challenge this method using more complex blends while performing the tests in an in-line manner.

Abstract

Monitoring powder potency and homogeneity are important in achieving real-time release testing in a continuous tablet manufacturing operation. If quality related issues are encountered, monitoring powder potency inside feed frame offers the last opportunity to intervene in the process before tablet compression. Feed frame monitoring methods based on near-infrared spectroscopy (NIRS) have been increasingly reported in recent years. New process analytical tools with the potential of being deployed alone or in combination with NIRS for feed frame monitoring are now available commercially. The present study evaluated the potential of near-infrared chemical imaging (NIR CI) for in-line monitoring of a prototype pharmaceutical composition containing ascorbic acid (AA), microcrystalline cellulose and dicalcium phosphate. NIRS was the reference method. In-line calibration models based on partial least square regression were developed and validated with a range of AA concentrations. The ability of NIRS and NIR CI (area scan) to predict concentrations in test runs was ascertained both independently and in combination. NIR CI (area scan), with a single bandpass filter, predicted AA concentrations – present at commercially relevant concentrations – with acceptable accuracy. Comparative results showed that NIR CI (area scan) has the potential for in-line monitoring of blend concentrations inside feed frames. In addition to the advantage of increased sample size, it also has the potential to detect segregation inside feed frames.

Keywords: NIRS; NIR CI (area scan); PAT; feed frame; in-line monitoring

Résumé français:

Le contrôle de la concentration et de l'homogénéité des poudres est important pour la réalisation libération en temps réel des lots dans une opération de fabrication de comprimés en continu. Si des problèmes liés à la qualité sont rencontrés, le contrôle de la concentration de la poudre dans le plateau d'alimentation de la presse offre une dernière opportunité d'intervenir dans le procédé avant la compression. Les méthodes de contrôle du plateau d'alimentation basée sur la spectroscopie proche infrarouge (NIRS) ont de plus en plus été rapportées ces dernières années. De nouveaux outils analytiques de procédés ayant le potentiel d'être déployés seuls ou en combinaison avec la NIRS pour le contrôle plateau d'alimentation sont maintenant disponibles sur le marché. La présente étude a évalué le potentiel de l'imagerie chimique infrarouge (NIR CI global) pour le contrôle en ligne d'une composition pharmaceutique prototype contenant de l'acide ascorbique (AA), de la cellulose microcristalline et du phosphate bicalcique. La NIRS a été la méthode de référence. Des modèles de calibration en ligne basés sur la régression par moindres carrées partielles ont été développés et validés sur une plage de concentration de l'AA. Les capacités de la NIRS et de la NIR CI (global) de prédire les concentrations lors des tests ont été vérifiées pour les deux méthodes séparément et en combinaison. La NIR CI (global), avec un unique filtre passe-bande, a prédit les concentrations d'AA – présent à des concentrations commercialement appropriées – avec une précision acceptable. Des résultats comparatifs ont montré que la NIR CI (global) a le potentiel pour le contrôle en ligne de mélanges de concentrations dans les plateaux d'alimentation. En plus de l'avantage de l'augmentation de la taille d'échantillon, elle a aussi le potentiel de détecter la ségrégation dans le plateau d'alimentation.

Mots-clés: Spectroscopie proche infrarouge (NIRS); l'imagerie chimique en proche infrarouge (NIR CI global); PAT; plateau d'alimentation; contrôle en ligne des concentrations

3.1 Introduction

Pharmaceutical regulatory authorities require compliance of every manufactured product batch with pre-approved specifications before its release to market. Compliance is crucial for the safety and efficacy of patient medications. Conventionally, the batch release takes place after all quality testing of representative samples has been completed, which could lead to considerable lag time and significant costs. The real-time release of pharmaceuticals is becoming possible by taking advantage of recent technological advances as well as recommendations from regulatory agencies for continuous process monitoring [105]. Product and process information collected during manufacturing can ensure that it complies with intended quality standards. Such information could be obtained by measuring the critical quality attributes (CQAs) of raw materials, in-process materials and critical process parameters (CPPs) during different manufacturing stages. Process analytical technology (PAT) tools enable CPP and CQA measurements in-line, on-line and at-line during the manufacture of different dosage forms, such as tablets, capsules, and liquids [2].

3.1.1 NIRS as PAT tool for tablet manufacturing

Pharmaceutical tablet production involves material handling through a series of steps, including sieving, mixing, particle size enlargement/granulation, drying, compression, sorting, and packing [106]. These different operations can elicit significant changes in material attributes which must be monitored to ensure final product quality. Near-infrared spectroscopy (NIRS)-based PAT applications have been developed for monitoring operations, like blending [36] [34] [107] [81], granulation [40][43][47], drying [44] [108] and continuous mixing followed by compression [59], coating [55] and end product testing [56][58][91][92], where it has proven to be advantageous over conventional in-process sampling and testing methods.

In addition to these key operations, consistent die-filling is important to meet tablet quality attributes. The feed frame helps maintain a constant supply of materials for die-filling during compression: it is the very last place to access powder just before compression. Powders undergo continuous shearing inside feed frames, which may cause component segregation [109]. From the real time release testing (RTRt) perspective, if blend concentration is ensured by meeting required specifications inside the feed frame, then monitoring tablet weight alone would be sufficient for tablet assay in RTRt. However, a number of undesirable phenomena

occurring inside the feed frame (e.g., material segregation) may impact final product quality [19]. Thus, process compliance inside the feed frame is a must to determine final product quality.

Continuous material movement inside the feed frame evokes significant changes in physical properties (e.g., density) which, in turn, poses a challenge for the development of successful PAT methods for in-line feed frame monitoring [60]. Such powder flow phenomena occurring inside the feed frame, e.g. density variations [15] and segregation [52], have been explored with NIRS. Despite challenges related to sample presentation, NIRS has been useful in in-line concentration monitoring inside the feed frame [15][16][61].

3.1.2 Near-infrared chemical imaging (NIR CI) in feed frame monitoring

The effective sample size is an important parameter for successful in-line feed frame monitoring. In a NIRS-based powder sample testing, it can be estimated with certain parameters, such as NIR beam diameter, its penetration depth and powder density [35][110], NIRS-based PAT methods verify content uniformity based on a small blend area (i.e., often a circular expanse 4-6 mm in diameter) illuminated by NIR beam [35]. Because of low sample scrutiny levels, it is possible for segregation, if present, to remain unnoticed. This limitation may be eliminated by NIR CI, which acquires chemical information over larger sample areas (e.g., 5×2 cm) using larger sensor arrays (e.g., 256×320 pixels) as compared to NIRS probes (e.g. 128×1 pixels). In addition, spatial and spectral information could potentially enhance process understanding as well as impart confidence in process data interpretation, e.g., for end-point determination of blending [63][65][39][68]. NIR CI-based applications developed with the aim of pharmaceutical quality assurance have been successful in analyzing the distribution of ingredients in tablets [64][74][73], their content uniformity [70], dissolution rates [111] as well as testing for counterfeit products [112] [113]. To the authors' knowledge, NIR CI for in-line feed frame monitoring has not yet been reported.

The main purpose of the present study is to determine the operational feasibility of NIR CI in a dynamic feed frame environment with a bench top feed frame set-up. NIR CI, with selected wavelength band filters, gives greyscale images that could help monitor the concentration and spatial distribution of NIR-active materials. NIRS served as a reference method, validating the state of mix and NIR CI results since it has already been undertaken for feed frame monitoring [114]. Sample volume was estimated both for NIR CI and NIRS. NIR

data were evaluated for qualitative and quantitative differentiation of powder blends according to various ascorbic acid (AA) concentrations. AA values with NIR CI were compared against NIRS and combined NIRS/NIR CI data. NIR CI potential to quantify segregation was also assessed. Its capability could constitute a major advancement in feed frame monitoring.

3.2 Materials

All samples in this study consisted of AA (DSM, Jiangsu), microcrystalline cellulose (MCC, Avicel PH 101[®], FMC biopolymer) and dicalcium phosphate (DCP, Di tab[®], Innophos) at different relative AA concentrations. MCC, DCP and AA particle sizes were 77-156, 150-420 and 150-850 μm , respectively. Particle size specifications according to supplier certificates of analysis were: d90 within 77-156 for MCC, d80 within 150-425 for DCP, d70 within 150-850 and d20 above 850 μm for Ascorbic acid. All the materials used in this study were taken from a single lot of respective materials thus particle sizes were essentially maintained constant, however significantly varying particle sizes between different lots of any of the materials may impact the performance of calibration model.

3.3 Methods

3.3.1 NIR penetration in samples

Sample volume estimation is important to ensure the required level of scrutiny for blend homogeneity [26]. In addition, regulatory specifications of tablet uniformity are dependent on the number of units sampled. Sample volume estimation in feed frame monitoring is necessary to predict tablet uniformity based on feed frame concentrations.

Sample volume could be estimated for each NIR CI (area scan) and NIRS measurement with the following equation 3.1 [26]:

$$\text{Sample volume} = A \times B \times C \quad (3.1)$$

where A is the sample area tested by the respective tool, B is NIR penetration depth, and C is sample bulk density.

NIR penetration depth inside samples is required to ascertain feed frame sample volume. A modified experimental protocol was set-up for this purpose based on the variable layer thickness method proposed by Berntsson et al [110]. They have reported that sample reflectance increases with increasing powder thickness until the latter reached an optically-thick level. Changes in reflectance at different powder thicknesses could be traced as a result

of NIR penetration in samples. In the present work, repeated NIR CI (area scan) at 2 mm and higher thickness showed no differences in pixel intensities: thus, this thickness was considered as equal to or greater than that of optically-thick samples. Actual NIR penetration was determined by comparing pixel intensities at lower than 2-mm thickness to 2-mm or higher sample thickness.

A plastic tray (Figure 3.1a) 5×4 cm in size was cast and divided into 2 halves (sections 1 and 2). These 2 halves were identical except for their depth, which differed by 2 mm (Figure 3.1b). The purpose of this set-up was to compare pixel intensities acquired from sections 1 and 2. When sufficient powder is placed in the tray, both sections should present similar responses in terms of pixel intensities; if not, the base of the tray will impact the signal of the shallower section (more NIR light will be reflected back to the NIR camera sensor if the light passes through the sample to the reflective surface of the base, thus pixels will have higher intensity).

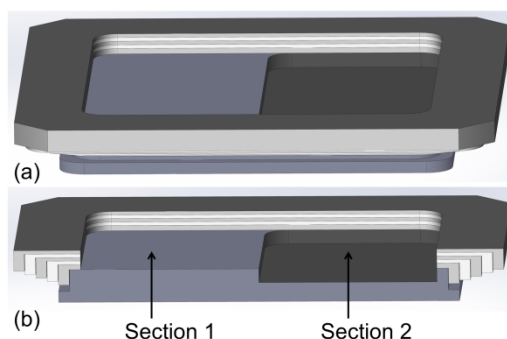


Figure 3.1: Sample tray (a) complete view, and (b) cross-section

Tray lids of different thickness (0.5, 0.75, 1.0, 1.5, 2.0 and 2.5 mm) were cast. When no lid was placed on the tray, section 1 had no depth, whereas section 2 was 2 mm deep. Section 1 depth becomes 0.5 mm with the 0.5-mm lid placed on the tray, while it becomes 2.5 mm for section 2. Each time a new lid was placed on the tray, sample material (AA particle size 354-420 μm) was filled in the tray and any excess above the tray lid level was gently scraped off.

3.3.2 Feed frame set-up

This study was conducted in the feed frame of a Manesty Novapress 37-station rotary tablet press. The experimental set-up comprised a fully functional feed frame without actual tablet compression. It helped to mimic powder movement in full-scale tablet manufacturing, but significantly reduced the amount of material and human effort required during trials. The feed frame consisted of 2 counter-rotating wheels (Figure 3.1a), each with 10 paddles. The second

wheel was located slightly lower than the first wheel to facilitate material movement inside the feed frame. The PAT tools NIRS and NIR CI (area scan) were placed above the second wheel (Figure 3.2b) just before the point where powder exits the feed frame and enters die cavities for compression.

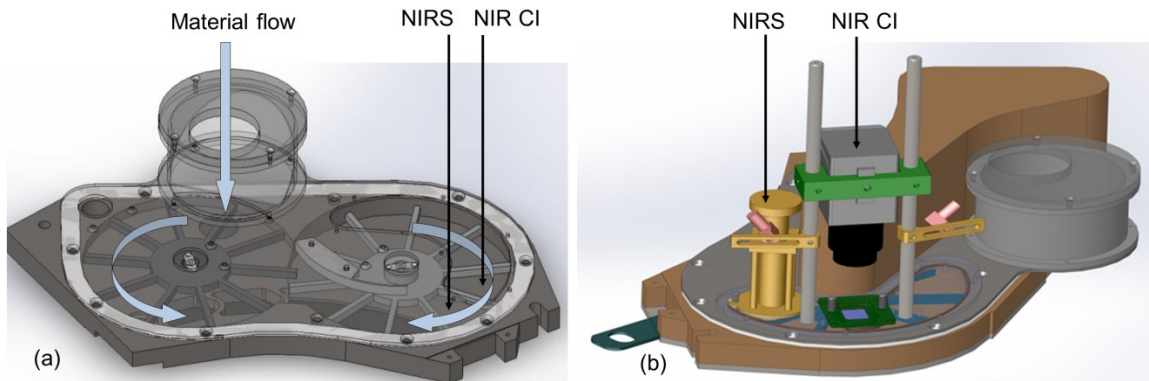


Figure 3.2: Feed frame set-up: (a) Material flow, and (b) NIRS and NIR CI (area scan) locations

3.3.3 Data acquisition inside the feed frame

Two data acquisition tools were employed: a NIR probe (MicroNIR 1700, Viavi Solutions, Inc., Milpitas, CA, USA) and a NIR camera-(Bobcat 320, Xenics infrared solutions, Leuven, Belgium) with 25-mm infrared lens (Navitar, Rochester, NY, USA). Both tools acquire NIR data in the 900-1,700 nm range, as described below.

3.3.3.1 NIR probe

The NIR probe was equipped with a spectroscope (resolution: 6.2 nm) that discretized spectrum into 128 levels. The probe's tip was slightly tilted in the direction of material flow, while keeping the observation window (5×15 mm) flat, and was mounted on a micrometer. This allowed the measuring tip to precisely touch the powder bed during measurements without reaching the paddle wheel. In this manner, NIR measurements helped to minimize baseline shifts due to powder wave behavior inside the feed frame, since there was no change in the path-length of the NIR radiation; however, baseline shifts due to changes in powder density caused by moving feed frame paddles were present.

3.3.3.2 NIR camera

The NIR camera was not equipped with a spectroscope: it integrated all energy levels into a single grey-scale image (320×256 pixels). However, different wavelength bandpass filters (Spectrogon Inc., Mountain Lakes, NY, USA) were affixed in front of the lens to capture narrow wavelength ranges chosen for specific active ingredients. Filters with wavelength ranges of 1240 ± 40 nm, 1460 ± 11 nm, 1600 ± 63 nm and 1653 ± 19 nm were tested for their suitability to differentiate Ascorbic acid from other components of the powder blend in NIR chemical imaging. A suitable filter was expected to selectively allow passage of wavelength ranges absorbed by Ascorbic acid (where MCC and DCP do not show NIR absorbance) to the NIR camera sensor, thus image pixels representing Ascorbic acid would appear darker than the pixels representing other components of the blend. As a result, NIR chemical imaging in the present work refers to a grey scale NIR image captured over a selective NIR wavelength span. The set-up was adapted for proper and constant powder presentation. Moved around by the paddles, large crests and troughs were formed at the surface of the powder (Figure 3a, 3b), impacting image acquisition. As can be observed from the comparison of Figure 3.3a and 3.3c; NIR chemical image quality is hampered due to self-shading of material in the presence of crest and trough pattern caused by feed frame paddle wheel. A flat insert (2.5×5.0 cm) was added to the feed frame surface to constrain these variations in front of the camera to capture the moving powder surface (Figure 3.3c, 3.3d). It was positioned 2.5 mm inside the powder whereas the lower tip of the NIR probe was situated at 5 mm inside the powder.

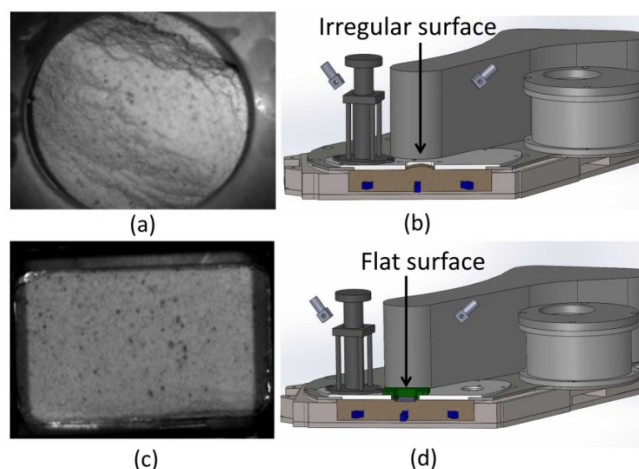


Figure 3.3: NIR CI (area scan) inside the feed frame: without a flat insert (a-top view, b-schematic vertical cross-section), and with a flat surface (c-top view, d-schematic vertical cross-section)

3.3.4 Formulations

Two sets of experiments, each with 7 samples (with different AA concentrations), were carried out on 2 different days. Both experiments analyzed the same concentrations, sample volume and blending time. AA concentrations were increased in a stepwise manner via 3% concentration increments between consecutive blends in order to develop the quantitative model. For the sake of simplicity, the first and second experimental sets will be referred to as trials 1 and 2. The purpose here was to prepare and validate quantitative models in trial 1 and to evaluate them for prediction of similar concentrations in trial 2.

Samples with 5 different concentrations (0, 3, 6, 9 and 12% w/w AA) from trial 1 were used for the development of the calibration model based on partial least square (PLS) regression.

Performance of PLS calibration model was tested in 3 ways:

- Test set I (300×76), with 4 and 8% w/w AA powder samples from trial 1, which represented model applicability for samples from the same trial.
- The test set II (300×76), with 4 and 8 % w/w ascorbic acid samples from trial 2, represented model applicability to test 1 concentration but in a second trial set.
- The test set III (750×76), with 0, 3, 6, 9 and 12 % w/w AA samples from trial 2, represented model applicability to concentrations as in calibration samples but in a second trial set.

(300 and 700 represent the number of samples while 76 represents the number of histogram bins in NIR CI (area scan), for NIRS 76 is replaced by 80 i.e. number of wavelengths)

Table 1 lists the different sample compositions analyzed in this study.

Table 3.1: Sample compositions in trials 1 and 2

Ingredients	Mass concentrations (% w/w)						
	Trial 1 – Calibration Trial 2 – Test III					Trial 1 – Test I Trial 2 – Test II	
Ascorbic acid	0.0	3.0	6.0	9.0	12.0	4.0	8.0
MCC	54.5	53.0	51.5	50.0	48.5	52.5	50.5
Dicalcium phosphate	45.5	44.0	42.5	41.0	39.5	43.5	41.5

Sample quantities were selected on the basis of feed frame working volume, obtained (550.0 g) by adding material slowly inside the closed feed frame until it was full and no more material was accepted inside. Samples were prepared by mixing excipients and AA granules together in a 3-liter V-blender (Patterson Kelley Blend Master, East Stroudsburg, PA, USA.) for 10 min. Blending time was kept constant for all samples to ensure uniform blending. The samples were charged and circulated inside the closed feed frame for 10 min at 20 revolutions per minute (rpm) of the paddle wheels. In total, 200 signals (each of NIR spectra and NIR CI) were recorded at a rate of 1 acquisition per rotation of the paddle wheel.

3.3.5 Data acquisition

3.3.5.1 NIRS

Spectral integration time was 5 ms for NIRS signals, with 50 spectra averaged to obtain output signals. An external mechanism was triggered each time to initiate spectral acquisition. Before the acquisition, the NIR probe was calibrated between 0 and 100% reflectance. For the 0% set-up, a NIR spectrum was acquired in the absence of infrared light while for the 100% set-up, NIR spectrum was recorded pointing the NIR beam at 100% reflectance reference. Every raw spectrum (R) acquired during the trials was corrected (C) with the 0% and 100% reflectance standards according to equation 3.2:

$$C = \frac{(R-D)}{(B-D)} \quad (3.2)$$

where D is 0% reflectance (dark) and B is 100% reflectance reference (bright)

3.3.5.2 NIR CI (area scan)

Sample presentation to the camera was properly controlled to ensure image-to-image data comparability. Sample-to-camera distance, optics, illumination and sample surface settings were kept constant. In addition, all NIR images were corrected for NIR source intensity variation over time using a white reference. For this purpose, a white reference was placed across the vertical axis on one corner of the flat insert. A ratio between the mean intensity of all the pixels representing this white reference in the respective image and the first image was used to correct the respective image for variation in the NIR light intensity. This ratio was multiplied to all pixel intensities in the NIR chemical image being corrected.

Considering differences in the NIR absorption of AA and other components (MCC, DCP), a 1,632-1,671-nm filter was selected to capture NIR images since it offered a comparatively greater contrast in pixels representing AA and other components (other components reflected more at selected NIR wavelengths).

3.3.6 Data treatment

All NIR spectra and image data obtained from the trials were analyzed by in-house MATLAB Scripts as well as the PLS Toolbox (Eigenvector Research, Inc., Manson, WA, USA.). NIRS spectra were evaluated with different pretreatments, such as standard normal variate (SNV), Savitzky-Golay (SG) second derivative, mean centering and scaling to unit variance.

NIR spectra of all individual components combined other components and composite sample (12% w/w AA) were acquired (Figure 3.4a). The diffuse reflectance intensity of all ingredients (AA, MCC, and DCP) kept on increasing roughly to 1,614-1,651 nm and then decreased. However, distinct spectral features started to appear only after 1,100 nm as the other components (MCC, DCP) absorb less than AA.

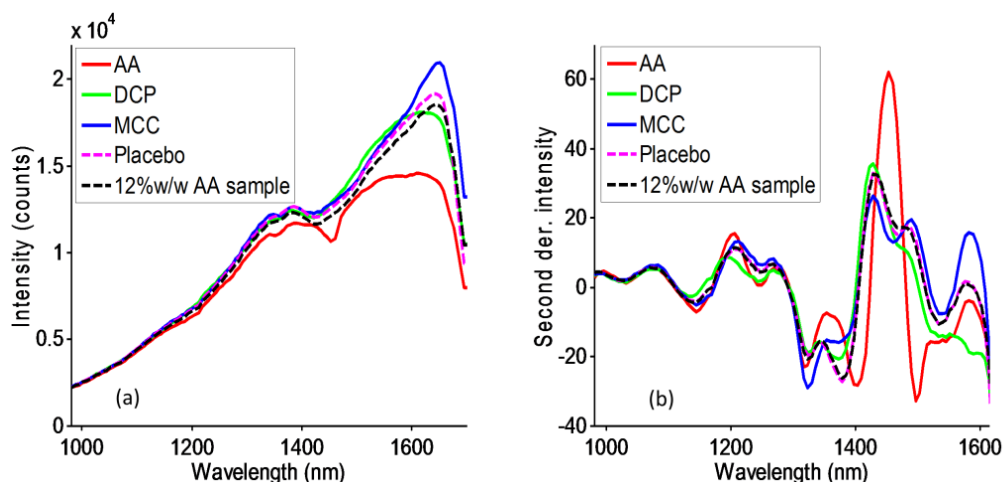


Figure 3.4: (a) NIR reflectance spectra of individual components and composite samples, (b) SG second derivative pretreated spectra of individual components and composite samples

Baseline shifts in raw spectra were removed to a significant extent as a result of pretreatments by SNV and SG second derivative (second order polynomial and 15 points). Color-coded plots of SG second derivative pretreated spectra (Figure 3.4b) in the 1,100-1,590 nm range revealed differences in the spectral signature of different samples over the entire range of selected spectra. As a result, all wavelengths in this spectral range were used in the principal component analysis (PCA) and further PLS analysis.

NIR chemical images with single filter do not contain any spectral information (as in the case of a spectrograph) but provide a 2D representation of the sample as seen over the particular wavelength band allowed by selected filter. Pixel intensities are influenced by the presence of NIR-active and NIR-non-active material: consequently, the distribution of pixel intensities could quantify content in a spectral format in a way similar to NIRS. Consequently, intensities of all pixels in NIR images were expressed in the form of intensity histograms, which classified them into different bins based on their intensity.

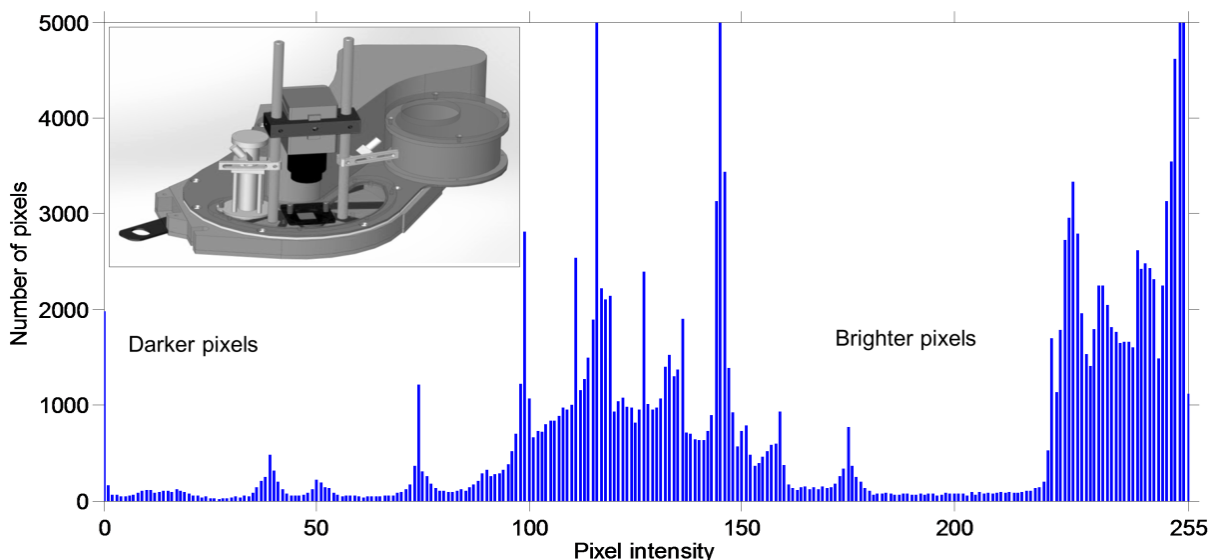


Figure 3.5: Histogram of a binary image

Figure 3.5 depicts the histogram of a grayscale schematic image of the feed frame in which the X-axis represents 8-bit image intensity, and the Y-axis embodies the proportion of pixels in each respective bin. Darker pixels are placed in bins close to the origin on X-axis while brighter pixels are placed away from the origin.

3.3.7 Data analysis by PCA and PLS

PCA and PLS were undertaken for data analysis. Initially, exploratory PCA was conducted to check if individual blend concentrations could be identified by respective signals. Thereafter, the quantitative relationship of NIR CI (area scan) with respective sample concentrations was evaluated against NIRS and the combination of NIR CI (area scan) with NIRS by PLS.

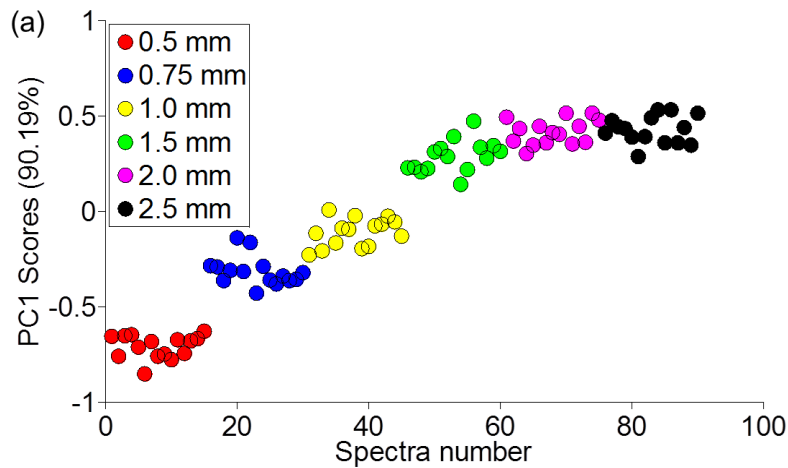
PLS models were statistically compared by R^2_{adj} (coefficient of determination in the calibration model), root mean square error of calibration (RMSEC) and root mean square error of cross-validation (RMSECV). 10 repeats were used in cross-validation. Root mean square error of prediction (RMSEP), the mean value and standard deviation of predicted concentrations were compared in tests 1, 2 and 3. In the end, the average NIR image of each sample blend and PLS concentration predictions were evaluated in different sections of NIR images.

3.4 Results and discussion

3.4.1 Sample volume

Sample volume was estimated by NIRS and NIR CI (area scan), starting with the assessment of NIR penetration. In the case of NIRS, multiple spectra were collected for analysis of each specific thickness sample (90×128). Spectral variations among different thickness samples were evaluated by PCA of complete spectra. SNV followed by mean centering was used as a spectral pre-treatment in order to maintain baseline variations caused by different levels of NIR light penetration. Principal component 1 (PC1), which represents 90.19% of total variance, explained the baseline variations seen among these spectra. PC1 versus sample plots (Figure 3.6a) showed that PC1 values kept on increasing with increasing sample thickness and later reached a plateau of around 1.5 mm in depth. Since there was no difference in spectra baseline beyond 1.5 mm thickness, it was concluded that NIR penetration, in this case, was 1.5 mm.

In the case of NIR CI (area scan), unpaired *t*-tests of pixel intensities were performed on 2 tray sections. The null hypothesis was rejected (at alpha value of 0.05) in samples 2.0-0.0 mm, 2.5-0.5 mm and 2.75-0.75 mm thick, but was accepted for all remaining thickness samples (3.0-1.0 mm, 3.5-1.5 mm and 4.0-2.0 mm), indicating that there were no differences in pixel intensities of the 2 sections with thickness more than 0.75 mm. Thus, it was concluded that NIR penetration in NIR CI (area scan) was 0.75 mm. Figure 3.6b depicts NIR images taken at different thickness combinations and corresponding pixel intensity histograms.



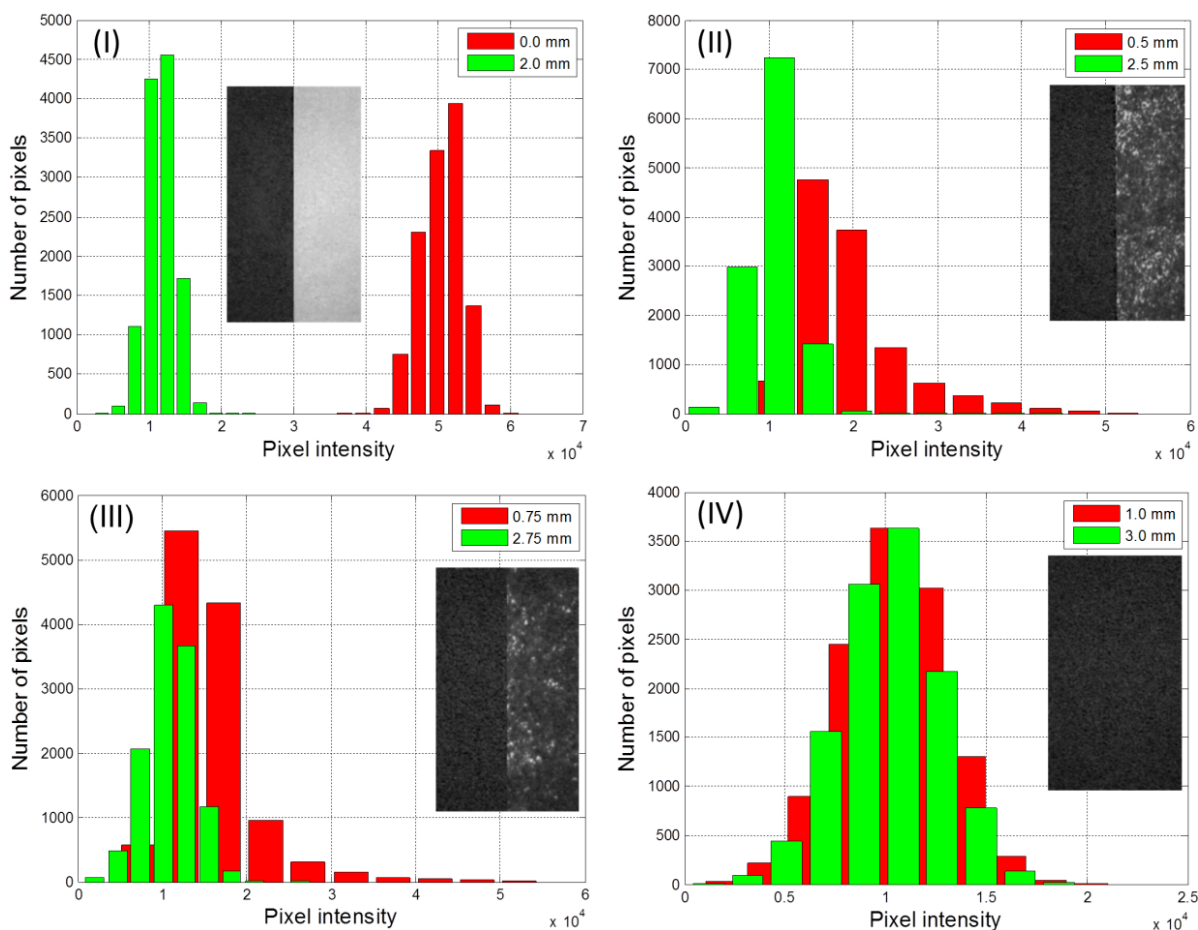


Figure 3.6: NIR penetration in samples: (a) PCA score plot NIRS, and (b) NIR CI (area scan) histogram

Bulk material density was found to be 0.48 g/cm^3 . Effective sample area was $3.5 \times 2.0 \text{ cm}$, as seen on NIR CI (area scan). Sample volume estimation was based on equation (1) for NIR CI and NIRS. It was found that the sample per image was 252 mg in NIR CI (area scan) while the sample per spectrum was 54 mg in NIRS. NIR penetration inside the sample was higher in NIRS than in NIR CI (area scan), however, sample volume with NIR CI (area scan) was estimated to be about 5 times higher than with NIRS. As an example, for a 250-mg tablet, each NIR CI (area scan) would represent a sample equivalent to tablet weight, but 5 spectra would be required to exemplify the same sample in NIRS. Considering the possibility of further increasing flat insert size, sample volume in NIR CI (area scan) could be adjusted to suitably represent tablet weight greater than 250 mg.

3.4.2 Qualitative NIRS analysis

Differentiation between calibration samples was evaluated by NIRS spectra collected inside the feed frame. PCA was performed on NIRS spectral data to highlight qualitative differences between the different samples. Savitzky-Golay (SG) second derivative, SNV followed by mean centering was used as spectral pre-treatment. The PCA score plot illustrated in Figure 3.7 shows clusters for samples with different concentrations.

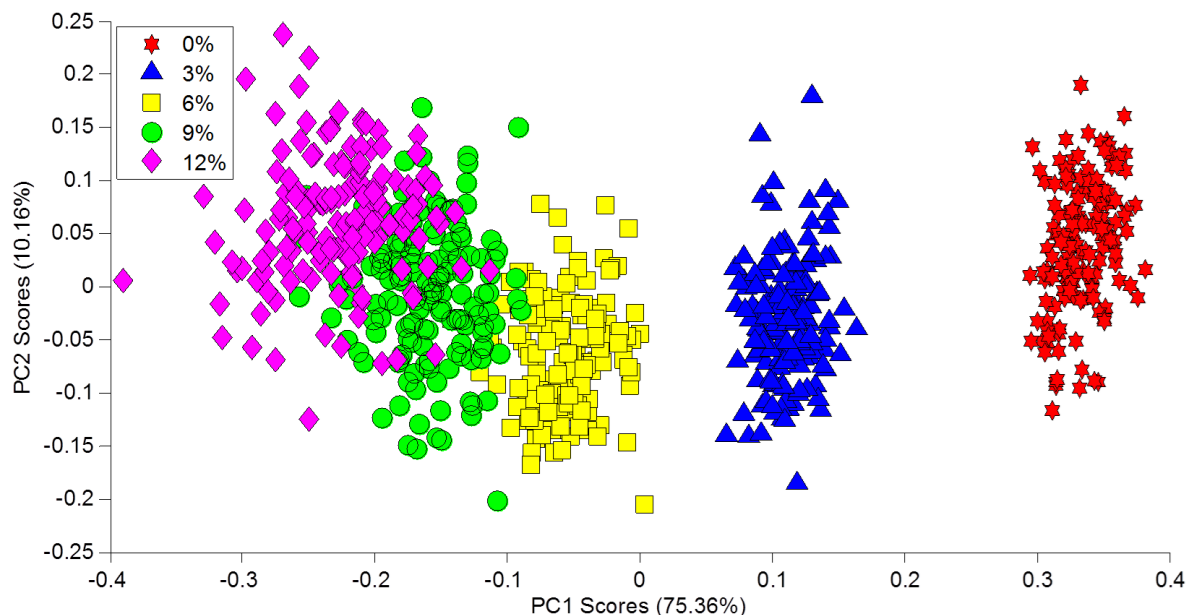


Figure 3.7: PCA score plots of NIRS data (Markers with different color represent % w/w content of ascorbic acid in the respective sample)

PC1 captured 75.36% of total variance while PC2 captured 10.16%. PC1 correlated with AA concentrations in samples on the basis of PC1 score versus sample plot. Samples with 0, 3 and 6% w/w AA were well separated. While still present, the separation between samples 6, 9 and 12% w/w was not as clear. However, it showed that with NIRS data, we can see a difference between the calibration samples. Because of this finding, it seemed reasonable to quantitatively analyze NIRS data (discussed in Section 2.5) but, first, differentiation of calibration samples in NIR CI (area scan) data needs to be done.

3.4.3 Qualitative NIR CI (area scan) analysis

NIR CI (area scan) data were converted to histograms before qualitative PCA. Separation of the samples into different groups based on NIR CI (area scan) data was compared with separation of these blends in NIRS data.

a) Histogram comparison in NIR CI (area scan)

The histograms of calibration samples in Figure 3.8 indicate that NIR CI (area scan) was able to distinguish samples with different AA concentrations.

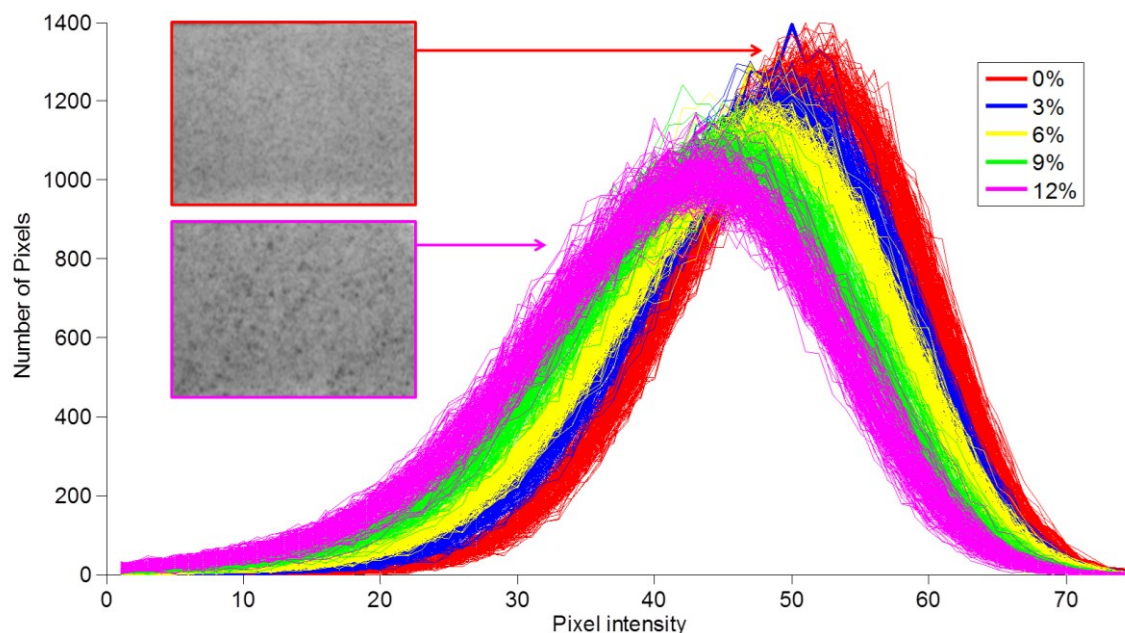


Figure 3.8: Pixel intensity histograms of calibration samples (Color represents % w/w content of ascorbic acid in the respective sample)

Two major trends were apparent in the comparative distribution of all histograms, i.e., vertical and horizontal shifts. All histograms were produced from same size images: thus, each histogram was made of the same number of pixels representing the sample. In this scenario, a vertical shift in histograms indicates an overall increase in the number of darker or brighter pixels based on the corresponding horizontal shift direction. A horizontal shift to the left suggests an increase in darker pixels, while a shift to the right signposts an increment of brighter pixels which, in turn, respectively correlate with higher and lower AA concentrations in samples.

Histograms of 0% w/w Ascorbic acid samples are located farthest of all on the right side and have the highest peak height, indicating the comparatively narrower distribution of brighter pixels. In contrast, histograms of 12% w/w samples are located farthest on the left with the lowest peak height, signifies a larger number of darker pixels and comparatively wide pixel distribution.

b) PCA with NIR CI (area scan)

The PCA score plot of histogram data (Figure 3.9) of calibration samples showed differences in the form of distinct cluster points. Mean centering and scaling to unit variance was used for data pre-treatment. PC1 captured 80.83% of total data variance and is correlated with AA concentrations in samples. 0%, 3% and 6% w/w samples were very well separated, but there was little overlap in 9 and 12% of them.

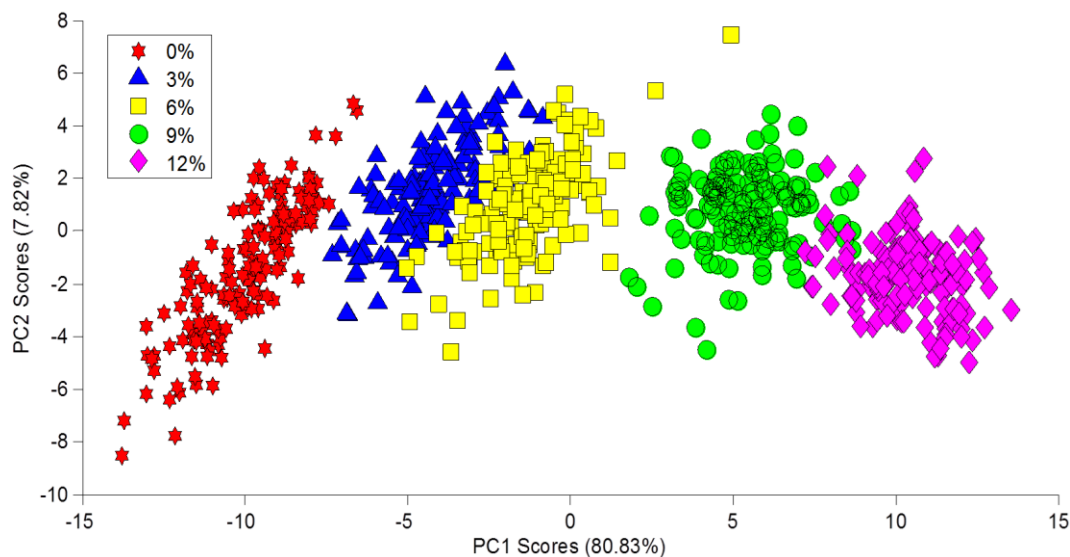


Figure 3.9: PCA score plot of NIR CI (area scan) (Markers with different color represent % w/w content of ascorbic acid in the respective sample)

In NIR CI (area scan), samples with 6, 9 and 12% w/w AA were well separated while 3 and 6% w/w AA samples were less clearly separated in contrast to NIRS data. However, individual observations in all samples show spread around the group cluster in both NIRS and NIR CI (area scan) data. Overall, PCA disclosed that NIR CI (area scan) was able to represent differences within calibration samples slightly better than NIRS because of larger sample size.

3.4.4 Quantitative analysis

The quantitative relationship between NIR CI (area scan) (750×76) and AA concentration was studied in PLS-based models. PLS-predicted concentrations in NIR CI (area scan) were compared with NIRS (750×80) and combined NIRS/NIR CI (area scan). A combined data matrix (750×156) of spatial and spectral information on each sample was obtained by horizontal concatenation of selected NIRS/NIR CI (area scan) data.

NIR CI (area scan) data were centered and scaled to unit variance before subjecting them to PLS modeling. The PLS model was developed with NIRS data, using SNV, SG

second derivative (second order polynomial and 15 points) and mean centering pretreatment. For PLS models with combined NIRS/NIR CI (area scan) data, respective data was pre-treated individually and then combined. NIRS data was pre-treated with SNV, SG second derivative (2nd order polynomial with 15 points), centered and scaled to unit variance, while NIR CI (area scan) data was centered and scaled to unit variance.

a) Quantitative model comparisons

All PLS models were cross-validated with random subsets during model development. Table 3.2 summarizes the different datasets of the PLS model parameters.

Table 3.2: Summary of PLS performance indicators

PLS model	Model parameters	PLS model		
		NIRS	NIR CI (area scan)	Combined (NIRS/NIR CI (area scan))
Calibration	R^2_{adj}	0.96	0.95	0.98
	RMSEC*	0.71	0.81	0.50
	RMSECV*	0.71	0.82	0.51
Test set I	RMSEP*	0.72	0.98	0.53
Test set II	RMSEP*	1.68	1.89	0.75
Test set III	RMSEP*	2.53	2.02	2.18
Number of latent variables		3	3	3

* PLS model errors were expressed in % w/w of ascorbic acid.

Overall, R^2_{adj} statistics of PLS models based on all 3 types of datasets (NIRS, NIR CI (area scan) and combined NIRS/NIR CI (area scan)) showed that PLS models fit well with calibration sample data. RMSEC and RMSECV values were higher in NIR CI (area scan), lower in NIRS, and even lower in the combined NIRS/NIR CI (area scan) model. For concentration prediction in trial 1 (test set I), the prediction error of NIR CI (area scan) was slightly higher than that of NIRS and the combined data model. Combining NIRS and NIR CI (area scan) did not improve concentration prediction in unknown samples.

Calibration models with respective datasets (NIRS, NIR CI (area scan) and combined NIRS/NIR CI (area scan)) elicited higher prediction error in trial 2 (test sets II and III) than in trial 1. However, the same calibration models with respective datasets (NIRS, NIR CI (area

scan) and combined NIRS/NIR CI (area scan)) predicted well in trial 1 (test set I), which had the same concentration as in test set II. Trials 1 and 2 were performed as separate runs on 2 different days: thus, higher prediction error could have been the result of variables in data acquisition (such as sample presentation, illumination, NIR source variability, random error) or due to actual variations in the samples. Since data acquisition was carefully controlled and both NIRS and NIR CI (area scan) simultaneously showed higher prediction error, it was likely that unidentified experimental variables caused actual variations (segregation) in trial 2 samples. However, this could be further evaluated on the basis of actual values of predicted concentrations.

b) Quantitative result comparisons

Unknown sample predictions with NIR CI (area scan), NIRS and combined NIRS/NIR CI (area scan) data models were compared according to average prediction values and standard deviation. Table 3.3 summarizes the predicted concentrations of unknown samples in test sets I, II and III.

Table 3.3: Summary of PLS-predicted concentrations

Test sets	Measured concentrations of samples (Ascorbic acid % w/w)	The predicted average concentration of the sample (1 standard deviation)		
		NIR CI (area scan)	NIRS	Combined (NIRS/NIR CI (area scan))
I	4.0	3.32 (0.63)	3.84 (0.55)	4.06 (0.36)
	8.0	8.66 (0.77)	8.61 (0.60)	8.44 (0.49)
II	4.0	5.70 (1.10)	6.06 (0.58)	4.69 (0.36)
	8.0	8.20 (0.90)	10.78 (0.73)	7.45 (0.49)
III	0.0	2.10 (1.30)	1.18 (0.55)	3.04 (0.24)
	3.0	5.00 (1.20)	4.69 (0.51)	4.55 (0.41)
	6.0	8.00 (1.20)	8.25 (0.70)	6.05 (0.40)
	9.0	9.00 (1.30)	10.64 (0.77)	8.18 (0.47)
	12.0	11.20 (1.10)	12.06 (0.69)	8.74 (0.46)

In test set, I, average predicted concentrations with PLS models in all 3 test sets were within the limits of $\pm 1\%$ w/w. However, the standard deviation of predicted concentrations was lower with combined NIRS/NIR CI (area scan) than with individual NIRS and NIR CI (area scan). Between individual data models, NIRS showed a lower standard deviation than NIR CI (area scan). The distribution of observations in calibration and test samples can be seen in predicted concentrations versus sample plots of the NIRS/NIR CI (area scan) model (Figure 3.10). Individually, NIR CI (area scan) showed comparatively wider distribution around measured concentrations than NIRS and combined NIR CI (area scan)-NIRS predictions. This may have been due to the combined effect of the larger sample area, lower NIR penetration and the comparatively larger particle size of AA granules. Since NIR imaging mostly captured surface distribution, depending on granule size, partial or complete exposure of particles to the surface could possibly have led to differences in consecutive images. It should be noted that the differences were very small and mainly occurred in particular samples. Concentration differences between samples were very well captured at the 1% w/w level among calibration and test samples.

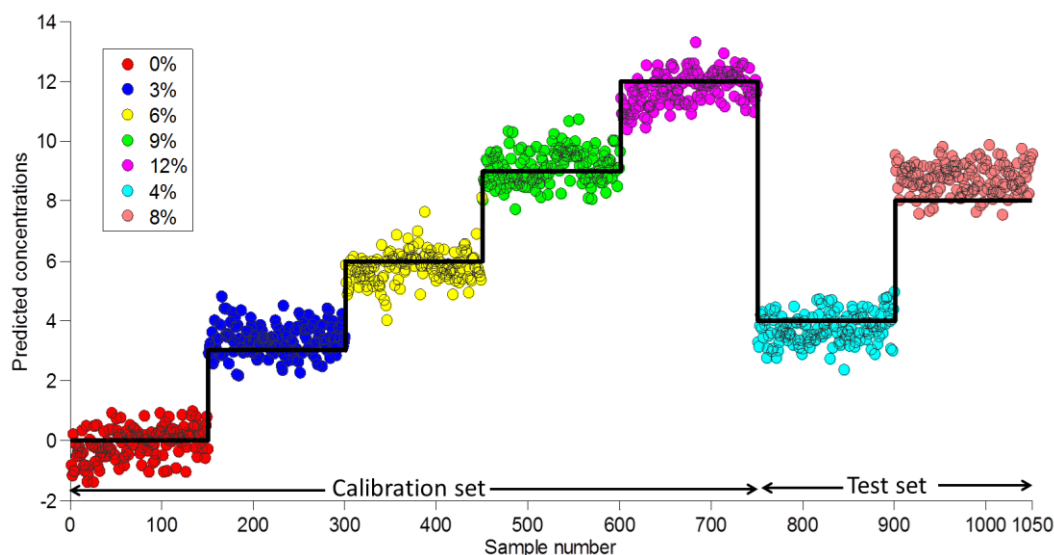


Figure 3.10: Predicted concentrations versus sample in test I with the combined NIRS/NIR CI (area scan) model (Color represents % w/w content of ascorbic acid in the respective sample)

In test set, I, mean values of predicted concentrations showed that the NIR CI (area scan)-based PLS model was in close agreement with the NIRS and combined NIRS/NIR CI (area scan) models. One of the major highlights of this work was that NIR CI (area scan) can

monitor feed frame concentrations in capacity at least equal to the already known PAT tool(NIRS) for feed frame monitoring. Combination of NIR CI (area scan) and NIRS data does not seem to offer any advantage over the accuracy of the NIR CI (area scan) and NIRS models except for precision (standard deviation) of the predicted values.

In the test set II and III concentration predictions, the standard deviation of predicted values followed the same trend (NIR CI (area scan) > NIRS > combined NIRS/NIR CI (area scan)) as in test set I. However, predicted concentrations were not very close to measured values. Average predicted concentration was found to vary in the range of $\pm 2\text{-}3\%$ w/w with all 3 types of data models.

PLS-predicted concentrations in trial 2 were expected to be close to those in trial 1 considering their exactly identical composition and blending time (i.e., 10 min). However, in the NIR CI (area scan) data, few samples (8%, 9% and 12% w/w) were predicted close to measured values while others (4%, 0%, 3% and 6% w/w) were not well predicted. Similarly, NIRS and combined NIR CI (area scan)/NIRS gave a prediction error of about 2-3% in all samples, except for 12% w/w. Since sources of possible variation in NIRS data were removed by suitable data pretreatments, prediction bias veered towards other variables, influencing the NIRS data. This hints at another possibility: that there could have been actual variations within samples in trial 2, which might lead to variations in predictions. In the present case, tablet compression was not performed subsequently: otherwise, these variations could have been tested by tablet assay. However, NIR CI (area scan) could still be useful to further probe variations of predicted concentrations in trial 2, since changes in local concentrations could be studied.

3.4.5 Average sample image analysis

The average NIR image of each sample was calculated in both trials 1 and 2. Considering the same mixing time, sample composition, particle size and operation parameters at the feed frame in both these trials, uniform, average images of individual samples were expected. Trial 1 produced uniform average images, but differences in average image intensity were observed in trial 2 (Figure 3.11a-f). The horizontal axis is essentially parallel to the paddle radius with the left side of the image located near the center of the paddle wheel.

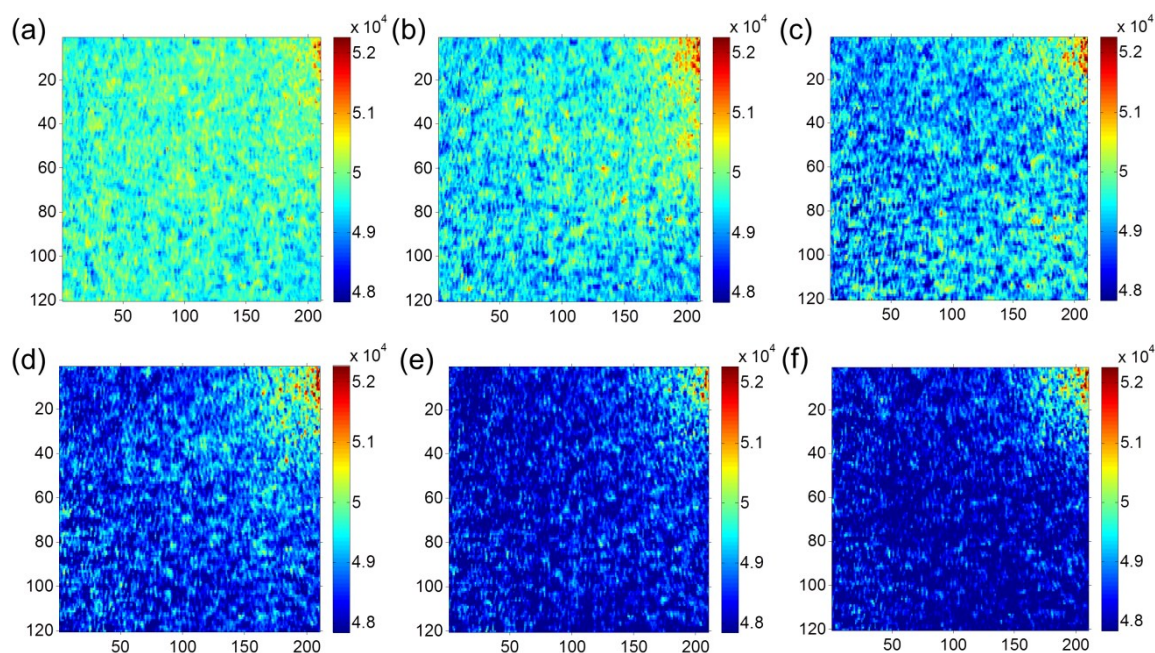


Figure 3.11: Trial 2 average sample images (a-f represent the average image of 3%, 4%, 6%, 8%, 9%, and 12% w/w ascorbic acid samples respectively, The blue to red color bar represents decreasing pixel intensity)

Average color-coded imaging established that the pixel intensity of average images changes progressively in samples from lower to higher AA concentrations. At the same time, pixels located in the upper right corner displayed higher intensity compared to the rest of the image. This could potentially indicate lower AA content in the upper right side of each sample. However, it was merely a qualitative observation, and quantitative analysis was used to confirm local variations in AA concentrations.

Each image was divided into 4 equal sections (Figure 3.12), and PLS concentration predictions were made for different image sections.

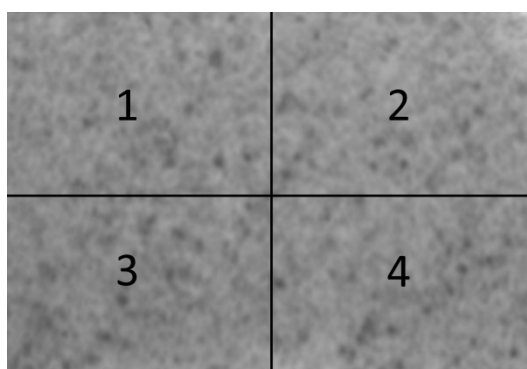


Figure 3.12: Subsections of the image used in the PLS analysis

Here, sections 1 and 3 represent the center of the feed frame, while sections 2 and 4 represent the circumferential side of the feed frame. Table 3.4 enumerates different image sections and respective average predicted concentrations.

Table 3.4 : Average predicted concentrations in different image sections

Sample (% w/w)	PLS-predicted sample concentration (1 standard deviation)				
	Section 1	Section 2	Section 3	Section 4	Average
3.0	3.96 (1.62)	0.61 (1.30)	5.28 (1.28)	1.92 (1.17)	2.94 (1.34)
4.0	4.69 (1.39)	1.43 (1.14)	5.22 (1.09)	1.51 (1.11)	3.21 (1.18)
6.0	7.04 (1.50)	2.49 (1.35)	7.50 (1.19)	4.87 (1.15)	5.47 (1.30)
8.0	9.31 (1.56)	5.76 (1.45)	9.53 (1.19)	7.84 (1.37)	8.11 (1.39)
9.0	10.40 (1.45)	6.78 (1.52)	10.65 (1.12)	8.73 (1.21)	9.14 (1.33)
12.0	8.79 (1.52)	7.23 (1.64)	11.61 (1.05)	10.78 (1.19)	9.92 (1.35)

It was observed that the section representing the upper right side corner of the image (section 2) consistently exhibited lower concentrations in all samples. Section 2 was followed by section 4, showing next lower concentrations. In contrast, the lower left corner of the image (section 3) presented higher concentrations in all samples, followed by section 1. Standard deviation values in each particular section were also higher, which signified image-to-image variations in samples. This change of local concentrations in different sections further supports the possibility of AA segregation in trial 2.

3.5 Conclusion

The main aim of this study was to evaluate the possibility of NIR CI (area scan) as a PAT tool for in-line feed frame monitoring while using NIRS as the reference method.

AA concentration predictions with the NIR CI (area scan)-based PLS models were found to be similar to those of the NIRS model. NIR CI (area scan) is better positioned to view concentration modifications over larger sample areas, and different image sections can be analyzed separately in the event of localized concentration changes. In the present set-up, sample volume tested by NIR CI (area scan) was 5 times higher than NIRS. Considering the

possibility of adjusting flat insert size, there is still the prospect of further increasing the sample size to meet unit dose samples at feed frame.

The Comparative performance of the NIRS and NIR CI for feed frame monitoring is summarized below (Table 3.5).

Table 3.5 : Comparative summary of NIR CI and NIRS

Parameter	NIRS	NIR CI
Wavelength range	900-1701 nm	Based on selected NIR filter
Sampling area	15 x 5 mm	35 x 20 mm
NIR penetration	1.5 mm	0.75 mm
Sample size in present setup	0.54 mg	2.52 mg
Visual representation of sample	No	Yes
Segregation testing	Limited utility	Potentially useful
PLS model performance		
R^2_{adj}	0.96	0.95
RMSEC*	0.71	0.81
RMSECV*	0.71	0.82
RMSEP*	0.72	0.98

An in-line feed frame monitoring system (NIR CI (area scan)) could help to obtain quantitative as well as visual presentations of powder composition which could be useful for real-time process monitoring by machine operators, e.g., end of material or obstruction of flow, segregation events, etc. This study indicates that NIR CI (area scan) alone or in combination appears to be a promising tool for in-line feed frame monitoring. NIR CI (area scan)-based concentration predictions may prove to be more representative since they gather information from comparatively larger sample area compared to NIRS, however, further studies are required to support this hypothesis.

Acknowledgments

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CHAPTER 4 In-line monitoring of Ibuprofen during and after the tablet compression using NIRS

Title in French:

Suivi en ligne de l'Ibuprofen pendant et après la compression en utilisant la NIRS

Summary

Content:

Chapter 3 discussed the NIR CI (area scan) data acquisition methodology and compares its performance with NIRS using very simple blends. The concentration monitoring was performed in an off-line manner. Following this, NIR CI (area scan) is evaluated for its feed frame monitoring performance using a complex blend similar to the commercial composition used by the industrial partner running the in-line tests on the tablet press. In addition equivalency of feed frame to tablet, monitoring is evaluated by comparing the concentrations predicted by NIR CI (area scan) and NIRS inside the feed frame against the concentrations predicted by NIRS in simultaneously compressed tablet, stratified tablet sub-samples, and their UV spectroscopic assay values.

The signal-to-noise ratio in case of single filter NIR CI (area scan) for a complex blend was found slightly lower compared to NIRS while NIR CI (area scan) data over certain time range was lost due to electrical failure of experimental setup. Consequently, NIR CI (area scan) data was not presented in the submitted article; however it is presented in chapter 5.

Results:

NIRS-based concentration predictions inside the feed frame matched very closely with that of NIRS predicted average tablet concentrations (averaged to represent similar time frame). However, individual tablet concentrations showed a higher tablet-to-tablet variation which might have resulted due to variables related to NIR data acquisition, surface distribution of the active or actual concentration variations in the tablets. UV spectroscopic assay of some of the tablets also showed a similar level of variation indicating actual content variation.

Contributions to the thesis:

NIRS-based concentration predictions inside the feed frame were seen to adequately represent tablet concentrations giving confidence in feed frame monitoring for achieving higher quality control as well as helping in real-time release testing. In addition, NIRS was shown to capture low material levels inside the feed frame, helping in in-line qualitative process control.

Abstract

Near-infrared spectroscopy (NIRS) used as process analytical chemistry tool to monitor Active Pharmaceutical Ingredient concentrations during tablet manufacturing has been reported to enhance overall product quality assurance. NIRS applications in different manufacturing stages are facilitated by their ability to handle different sample presentations – be it solids, liquids, gels or powders. The present study evaluates NIRS suitability for monitoring Ibuprofen concentrations (coated pellets form) inside the feed frame of a tableting press as well as in output tablets. Process monitoring was undertaken with qualitative and quantitative chemometric analysis. NIRS-based predictions of concentrations both inside the feed frame and in tablets were compared to ultraviolet (UV) spectroscopy assays of temporally stratified tablet samples. Process dynamics were also compared in terms of concurrent concentrations change kinetics in the feed frame and in output tablets.

NIRS showed good sensitivity to Ibuprofen concentrations despite the use of coated pellets. Ibuprofen contents as low as 1.7% w/w were detected effectively. NIRS-based quantitative predictions in the feed frame and in tablets closely matched the UV assay values of sampled tablets. As anticipated from the 2-wheel feed frame geometry, upon the addition of each consecutive blend, results show that the predicted concentrations inside the feed frame were delayed compared with that of the tablets exiting the tablet press. For these tests, the delay was estimated to be 1.25 minutes. This finding highlights the importance of NIRS probe position inside the feed frame as a function of its geometry. Successive feed frame and tablet monitoring by NIRS could prove beneficial for real-time release testing of tablet formulations.

Keywords: NIRS; PAT; feed frame; tablet; chemometrics; real-time release testing

Résumé français: La spectroscopie proche infrarouge (NIRS) utilisée comme outil analytique de procédés pour le contrôle des concentrations des Ingrédients pharmaceutiques actifs durant la fabrication de comprimés a été rapportée comme améliorant l'assurance qualité globale du produit. Les applications de la NIRS dans différentes étapes de fabrication sont simplifiées par leur capacité de manipuler différents types d'échantillons – solides, liquides, gels ou poudres. La présente étude évalue l'adéquation de la NIRS pour le contrôle de la concentration de l'Ibuprofen (en forme de pastilles enrobées) dans le plateau d'alimentation de la presse à comprimer ainsi que dans les comprimés produits. Le suivi du procédé a été réalisé par analyse chimiométrique qualitative et quantitative. Les prédictions de concentrations basées sur la NIRS à la fois dans le plateau d'alimentation et dans les comprimés ont été comparées à des dosages obtenus par spectroscopie ultraviolette (UV) pour des échantillons de comprimés temporellement stratifiés. La dynamique du procédé a aussi été comparée en termes de cinétique de changements concurrents de concentrations dans le plateau d'alimentation et dans les comprimés produits.

La NIRS a montré une bonne sensibilité aux concentrations d'Ibuprofen malgré l'utilisation de pastilles enrobées. Des concentrations d'Ibuprofen aussi faibles que 1.7 % m/m ont été détectées. Les prédictions quantitatives basées sur la NIRS dans le plateau d'alimentation et dans les comprimés sont très proches des valeurs de dosages UV des comprimés échantillonnés. Comme anticipé pour la géométrie à 2-cuves du plateau d'alimentation, lors de l'addition de chaque mélange consécutif, les résultats montrent que les concentrations prédites dans le plateau d'alimentation ont été retardées comparées à celles des comprimés quittant la presse. Pour ces tests, le retard a été estimé à 1.25 minute. Ce résultat met l'accent sur l'importance de la position de la sonde NIRS dans le plateau d'alimentation comme fonction de sa géométrie. Le suivi efficace du plateau d'alimentation et du comprimé par NIRS peut être bénéfique pour la libération en temps réel des lots de comprimés.

Mots-clés: Spectroscopie proche infrarouge (NIRS); PAT; plateau d'alimentation; chimiométrique; test de libération en temps réel (RTRt)

4.1 Introduction

Tablet dosage forms constitute a major portion of pharmaceutical solid oral dosage formulations available in the marketplace. As per the US Food and Drug Administration's novel drug approval database, 23 of 45 new molecular entities were formulated as solid dosage forms in 2015, and 15 of the 23 were tablets [115]. Tablets offer patients ease of handling and administration while ensuring physicochemical and microbial stability benefits to manufacturers. Pharmaceutical organizations optimize tablet manufacturing in a product-specific manner and follow stringent quality checks in the entire production process. However, quality issues impacting product composition and safety still arise. A summary of recent product recalls highlights incorrect potency (hyper or hypo) and cross-contamination as leading quality problems [116]. Such quality failure events underline the importance of process monitoring in all stages of manufacturing. Process analytical technology (PAT) tools help to monitor different production stages, ensuring the quality of intermediate as well as finished products [2]. During tablet manufacturing, subsequent feed frame and tablet concentration monitoring could increase confidence in tablet quality assurance and help pinpoint the causes of failed batches.

4.1.1 PAT for in-line feed frame monitoring

Near-infrared spectroscopy (NIRS)-based PAT has been reported to be successful in tablet manufacturing operations, such as granulation [117][43], drying [44][108], blending [81][36] and coating [55]. NIRS transitioning from off-line testing to in-line monitoring at various stages of tablet manufacturing has been made possible through a better understanding of manufacturing processes and NIRS parameters. Feed frame monitoring offers the unique advantage of measuring powder potency immediately before tablet compression. Quantifying powder blend concentration inside the feed frame could also ensure that tablet concentrations are within specified limits.

Dynamic sample presentation inside the feed frame and other related variables, such as probe-to-powder/paddle distance, powder mass hold up, density changes due to paddle movement, paddle speed [15], as well as NIRS probe location [51], make in-line feed frame monitoring a challenging task. Ward et al. [16] reported correlations between NIRS signals and weight-corrected tablet assays at 3.5% w/w active concentration but suggested the need

for optimizing NIR probe location to avoid poor correlations at lower paddle speeds. Šašić et al. [61] demonstrated a linear relationship between the tablet potency and NIR spectral intensity at a single wavelength characteristic of the active pharmaceutical ingredient (API). They worked with 3.5% w/w API concentration and reported that this relationship cannot be satisfactorily applied to another trial because of spectral baseline variations in spite of the use of a 2nd derivative data pre-treatment. Mateo-Ortiz et al. [15] observed the superiority of in-line partial least squares (PLS) calibration over off-line models for 5-15% w/w Paracetamol blends inside the feed frame. Most of earlier studies involved discrete concentration blends at API levels equal to or higher than 3.5% w/w. Recent work by Durão et al [118] showed successful implementation of different PAT tools such as light-induced fluorescence (LIF), NIRS and red-green-blue (RGB) imaging for quantitative composition monitoring of a multi-vitamin powder blends inside the feed frame. Among the different components, NIRS precisely quantified Ascorbic acid and Ferrous fumarate in the concentration range of 5-15 and 2-8% w/w respectively. Implementation of NIRS-based quantitative concentration monitoring inside the feed frame requires a thorough feasibility study based on the specific tablet formulation, taking into account factors such as the range of concentrations. In addition, the capability of NIRS-based quantitative regression models to capture subtle concentration changes requires investigation to discern powder segregation inside the feed frame.

4.1.2 PAT for in-line tablet monitoring

Off-line NIRS applications testing tablets for assay [56], content uniformity [58] and dissolution [109] have been reported in the literature. Off-line analysis has shown good correlations of NIRS and tablet properties but could not be undertaken for tablet monitoring in routine manufacturing operations due to limitations of time and resources. In recent years, increased flexibility of technology has made in-line tablet monitoring possible, e.g., in-line tablet monitoring immediately after compression. Karande et al. [119] reported the results of tablet quality testing via NIRS immediately after ejection from the dies, but the compression process was operated at much lower speeds than used in commercial production. They employed a 10-station compression machine functioning at 10 turret rpm. Järvinen et al. [59] demonstrated successful monitoring of tablets containing 20-30% w/w API in a continuous direct compression process. They performed tablet NIRS scanning at much higher rates (25,000-125,000 tablets/h) on the turret. In NIRS data analysis, they studied the average

spectra of 10 tablets and obtained good model fit ($R^2_{\text{adj}} = 0.943$, RMSEC = 0.75% - root mean square error of calibration) as well as prediction (RMSEP = 1.37% - root mean square error of prediction). However, by so doing, the model lost the ability to detect variations in individual tablet spectra, which would be likely during high-speed industrial compression processes. In light of these findings, we investigated the individual NIR spectra of tablets in PLS calibration model preparation as well as in tablet concentration predictions.

During in-line tablet monitoring, size, shape as well as the high-speed movement of tablets on the turret can introduce spectral variations affecting the performance of quantitative models for monitoring concentrations. Thus, tablet NIRS testing, which simultaneously offers high-speed data acquisition and uniform sample presentation, needs to be evaluated. The present study reports on tablet NIRS testing at the end of tablet compression but before their final packaging.

4.1.3 PAT for combined feed frame and tablet monitoring

The objective of the present work is to evaluate the feasibility of using NIRS for in-line concentration monitoring (qualitative and quantitative) inside the feed frame as well as in the compressed tablets during tablet manufacturing process. To achieve this, 2 NIR probes were used. The first probe (Viavi PAT-U) was located inside the tablet feed frame to scan the flowing powder while the second (VisioNIR) was located downstream of the tablet press to scan the resulting tablets. In order to verify the performance of the in-line NIRS probes, off-line tablet analysis of selected tablet samples was performed using a standalone NIRS system (Bruker MPA) and UV assay tests.

This work specifically focuses on evaluating the feasibility of NIRS for in-line monitoring of Ibuprofen concentrations in the form of polymer-coated pellets inside the feed frame and in compressed tablets. Ibuprofen concentrations were predicted by partial least squares (PLS) regression models. The accuracy of NIRS (including data modeling) to detect varying Ibuprofen concentrations was verified by comparing NIRS-predicted tablet concentrations through UV assays of selected tablet samples collected at respective time intervals. NIRS-tested sample volume inside the feed frame was estimated and compared to equivalent tablet samples.

Another objective is to study the kinetics of Ibuprofen concentration changes inside the feed frame and in the tablets for a set of given operating parameters in a tablet compression

machine. Ibuprofen concentrations inside the feed frame were altered from one blend to another by adding different blends successively in a predefined sequence in the hopper. As a result, concentration step changes presented a transition phase followed by a plateau for each new blend. Monitoring concentration kinetics during these phases is expected to help understand material mixing, die filling and material propagation inside the feed frame.

4.2 Materials

The materials used in this study comprised Ibuprofen-coated pellets (Adare Pharmaceuticals, Vandalia, OH, USA), mannitol (Roquette, Keokuk, IA, USA), microcrystalline cellulose (Avicel® PH 101, FMC BioPolymer, Philadelphia, PA, USA), sodium starch glycolate (Roquette, Lestrem, France), colloidal silicon dioxide (Aerosil® 200 Pharma, Evonik Corporation, Parsippany, NJ, USA) and magnesium stearate (Mallinckrodt, St. Louis, MO, USA). Analytical grade reagents were used for UV spectroscopy testing of tablet samples.

Particle size specifications of the ingredients are given here. For Ibuprofen pellets, 2% of the total mass was retained on mesh 40 (420 μm) while 5% of the total mass was passed through mesh 80 (177 μm). For mannitol, 87% of the total mass was retained on mesh 140 (105 μm) while 12 % of the total mass was retained on mesh 35 (500 μm). In case of microcrystalline cellulose, 95% of the total mass pass through mesh 120 (125 μm) while 68% of total mass retained over mesh 325 (45 μm)

4.2.1 Formulation composition

Tablet composition in the present work consisted of different Ibuprofen concentrations available in pellet form coated with gelatin and cellulose acetate phthalate. Five blends were prepared with different contents of Ibuprofen pellets. All excipients other than magnesium stearate compensated for the change in weight of Ibuprofen pellets, as indicated in Table 4.1. Excipient concentrations were varied in proportion to the Ibuprofen level of the respective blend while magnesium stearate was maintained at the same concentration in all blends. Batch size was set at 12.0 kg because of equipment capacities, desired tablet compression rate and time required for concentration stabilization inside the feed frame. All ingredients except magnesium stearate were added in the V blender (Patterson Kelley, East Stroudsburg, PA, USA) and rotated for 15 min at 26 rpm. Magnesium stearate was then included, and mixing

was continued for 2 additional minutes. At the end of mixing, all blends were transferred to a double-lined polythene bag for tablet compression.

Table 4.1: Formulation composition with five different Ibuprofen levels (all concentration values are in % w/w)

Ibuprofen pellette	0.00	2.00	8.00	15.80	18.00
Mannitol	82.37	80.40	75.66	69.12	67.4
Microcrystalline cellulose	11.85	11.80	10.96	10.06	9.70
Colloidal silicon dioxide	2.39	2.40	2.19	2.01	1.95
Sodium starch glycolate	2.39	2.40	2.19	2.01	1.95
Magnesium stearate	1.00	1.00	1.00	1.00	1.00

As listed in Table 1, Ibuprofen pellet contents were varied in the range of 0-18% which, in reality, corresponded to 0-15.3% w/w Ibuprofen, considering pellet assay value (85% w/w Ibuprofen). However, the blends are referred herein by % w/w Ibuprofen pellet contents. Random blend order was adopted during tablet compression, i.e., Ibuprofen blends were added to the hopper in 2, 8, 18, 0 and 15.8% w/w sequence. Consequently, the smallest step change was 6 % w/w (from 2 to 8 % w/w) while 18 % w/w (from 18 to 0 % w/w) was the largest. Such a sequence was purposefully adopted to check NIRS responses to the lowest and highest concentrations inside the feed frame as well as to clearly outline the 5 steady states and help quantify step-change dynamics.

4.3 Equipment and Methods

Three NIR probes (Viavi inside the feed frame, VisionNIR for in-line tablet testing and Bruker for subsequent off-line tablet testing) with different specifications of NIR range, spectral resolution and integration time were used. Data acquisition parameters of respective NIR probe are summarized in table 4.2.

Table 4.2: NIR spectral acquisition parameters

NIR probe	Location	Spectral range (nm)	Spectral Resolution (nm)	Integration time per spectrum (ms)	Number of spectra averaged	Total integration time (ms)
Viavi PAT-U	Inside the Feed frame	915-1701	6	5	50	250
Bruker MPA	Off-line tablet testing	800-2778	0.5	354	32	11,328
VisionNIR	In-line tablet testing	850-1650	3	0.5	-	0.5

Details of the NIRS probe set-up are provided in the following sub-sections.

4.3.1 Feed frame monitoring (in-line)

A Manesty Novapress 37-station rotary tablet press with feed frame was employed in this study. Details of feed frame design appear in an earlier publication [20].

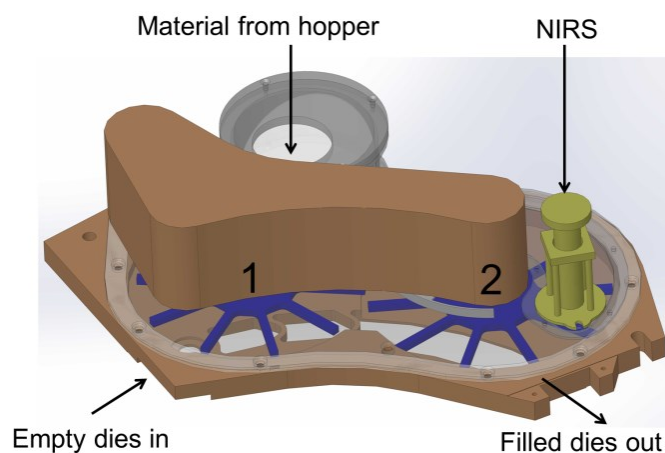


Figure 4.1: NIRS location on the feed frame

A NIRS probe (Viavi PAT-U) was placed above the second wheel just before the point where powder exits the feed frame (Fig.4.1) and enters the die cavities for compression. The NIR probe tip was positioned with a micrometer 6 mm above the paddle wheel to ensure its contact with the powder while preventing contact with the paddle wheel. Data acquisition was

triggered by a sensor attached to the feed frame shaft. One NIR spectrum was recorded at each rotation of paddle wheel. NIRS probe parameters and acquisition settings are listed in Table 4.2.

Tablets were compressed at a rate of 23,460 tablets/h. Feed frame paddle wheel rpm was adjusted at 13 rpm to obtain consistent tablet weight. Temporally stratified tablet samples (at intervals of 1 min in the stable phase and 15 s for 4 min 30 s in the transition phase) were collected during the entire compression cycle. Stationary and transition concentration phases were calculated on the basis of machine rpm, tablet weight and a total number of punch sets. 312 tablets were sub-sampled to obtain 3 tablets per min from the samples collected during each stable phase. These 312 tablets are referred to as “tablet sub-samples” throughout this paper. The sub-samples were tested for Ibuprofen pellet content, by off-line (Bruker MPA) and in-line NIRS (VisioNIR) as well as UV spectroscopy.

4.3.2 Tablet-monitoring (in-line)

A Teonys tablet-sorting machine (Proditec, Pessac, France) equipped with a line scan camera provided in-line tablet-monitoring. It was adapted to hold a NIRS probe (VisioNIR, Visiotec GmbH, Laupheim, Germany) for tablet NIRS scanning. All compressed tablets and sub-sampled (312) tablets were scanned in reflectance mode using acquisition parameters as shown in table 4.2. Tablets were passed below the NIRS probe on a conveyor belt. The tablet scanning rate depended on their distribution along the conveyor belt by the distribution system and the tablet dimension. Conveyor belt speed was set at 350 mm/s in the present work, resulting in NIRS scanning 10,800 tablets/h.

4.3.3 Tablet testing (off-line)

A Bruker NIRS stand-alone system (Bruker multi-purpose analyzer, Bruker optics ltd, Milton, ON, Canada) provided off-line tablet NIRS analysis. All of the sub-sampled 312 tablets were manually scanned in diffuse reflectance mode using acquisition parameters shown in table 2.

Ibuprofen contents in the tablet sub-samples were quantified by a UV method. A UV-visible spectrometer (Ultrospec 2100 pro, Biochrom Ltd., Holliston, MA, USA) was used for wavelength selection and recorded the UV absorbance of tablet sample solutions. The aqueous solution of Ibuprofen pellets showed maximum UV absorbance at 264 nm wavelength. Thus,

the UV absorbance of all calibration standard solutions and each tablet sample solution was measured at the same wavelength (264 nm). The calibration curve prepared with standard solutions containing Ibuprofen concentrations in the range of 50-1500 µg/ml showed a regression coefficient of 0.9996, indicating good linearity between Ibuprofen concentrations and UV absorbance responses. The Ibuprofen contents (% w/w) of respective tablets were ascertained from this calibration curve. Solutions of 15.8 and 18% w/w Ibuprofen tablets were diluted to suitable concentrations to fall within the range of the calibration curve. The % w/w Ibuprofen pellet contents of each tablet were calculated by considering sample dilution factors as well as respective tablet weight.

4.3.4 NIRS data acquisition and pre-treatment

Before spectral data acquisition, the NIR probes were calibrated between 0 and 100% reflectance. A NIR spectrum was acquired for the 0% set-up in the absence of infrared light, while a NIR spectrum was recorded for the 100% set-up by pointing the NIR beam at 100% reflectance reference. Every raw spectrum acquired during the trials was corrected with the 0% and 100% reflectance standards according to equation 4.1:

$$C = \frac{R-D}{B-D} \quad (4.1)$$

where C is the corrected spectra, R is the raw spectra, D is the 0% reflectance (dark) standard and B is the 100% reflectance (bright) standard.

NIR spectra collected inside the feed frame contained Ibuprofen concentration information. In addition, they were influenced by other variables, such as material movement and particle size differences. In tablets, spectral signatures are influenced by tablet shape and surface (oblong or concave) as well as by small variations in hardness. Spectral pre-treatments, such as standard normal variate, Savitzky-Golay second derivative, multiple scatter correction (MSC), centering and scaling to unit variance were evaluated before performing the qualitative and quantitative analysis. MSC followed by mean centering was selected as the optimum spectral pre-treatment for feed frame as well as tablet NIR spectra by comparing principal component analysis (PCA) parameters (score values and percent variance explained) for different spectral pre-treatments.

4.3.5 NIRS wavelength selection

The present work evaluated different regions of NIR spectra for inclusion in the qualitative and quantitative analysis of Ibuprofen content. NIR reflectance spectra of Ibuprofen pellets, Placebo blend (all components of tablet composition except Ibuprofen) and 18% w/w Ibuprofen blends were recorded using Viavi PAT-U NIR probe. When plotted together, these spectra showed characteristic peaks of pure Ibuprofen pellets and their expression to a different extent in Placebo and 18% w/w Ibuprofen blend spectra (Fig.4.2). Characteristic peaks of pure Ibuprofen pellets were masked significantly in the composite blend, still, spectra in the range of 1100-1250 and 1350-1700 nm showed differences in the placebo and 18% w/w Ibuprofen blends.

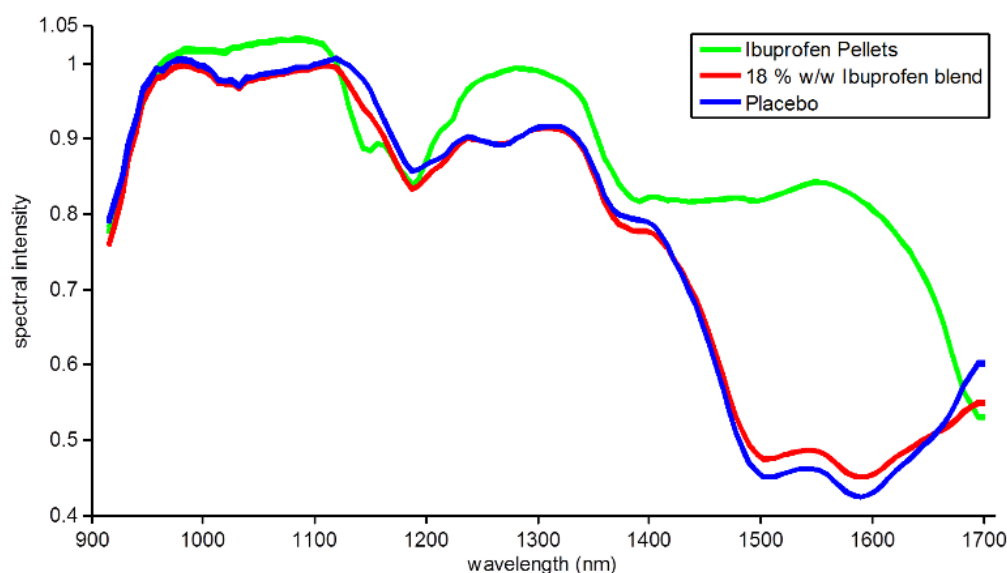


Figure 4.2: Raw NIR reflectance spectra of Ibuprofen pellets, placebo, and 18 % w/w Ibuprofen blend compositions

The pre-treated NIR spectra of respective powder and tablet samples, representing different % w/w Ibuprofen concentrations, were compared visually for all NIRS measurements (off-line tablets, in-line feed frame, and in-line tablets). Spectral regions showing the greatest intensity variations, in response to varying Ibuprofen concentrations, were evaluated for inclusion in qualitative and quantitative chemometric models. In the case of off-line NIR spectra of the tablet sub-samples, different spectral regions were compared on the basis of RMSE- root mean square error between PLS regression-predicted Ibuprofen concentrations and UV assay values of respective tablets. For in-line feed frame spectra, different spectral selections were compared on the basis of percent variance explained and score values versus

sample trends in PCA. The wavelength range for in-line NIR spectra of tablets was selected for off-line NIR spectra of tablets.

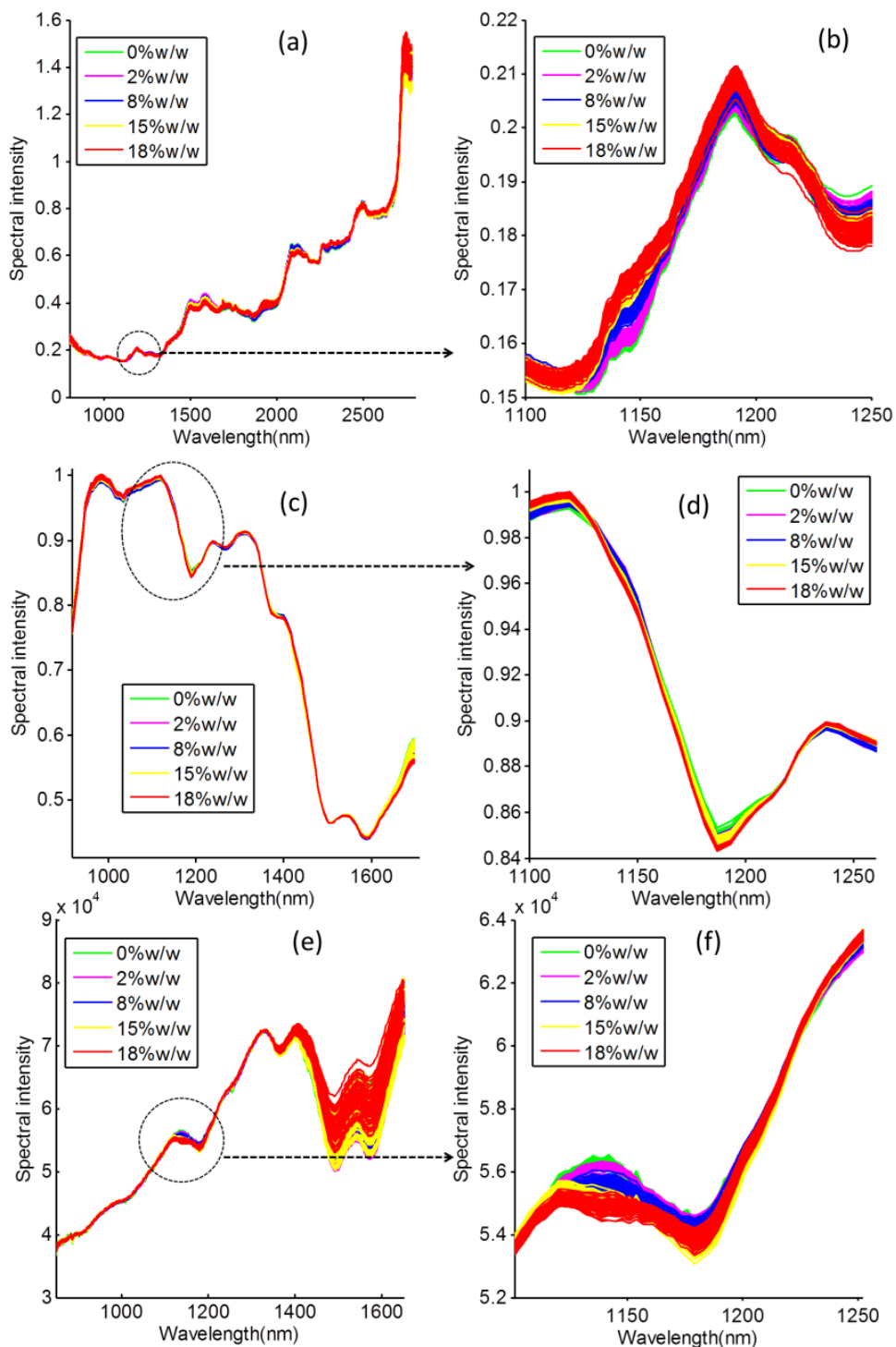


Figure 4.3: MSC treated full NIR spectra and a selected range of 1100-1250 nm for off-line tablet analysis (a-b), feed frame analysis (c-d) and in-line tablet analysis (e-f) respectively.

Off-line NIRS tablet analysis (Bruker) offered higher spectral resolution and larger wavelength spans than in-line feed frame and in-line tablet NIRS. Based on visual inspection of MSC treated full NIR spectra (Fig.4.3a), spectral data in the range of 1100-1250 (Fig. 4.3b), 1321-1500, 1600-1901, 2101-2701, 1100-2701 nm and combined data on multiple selections were evaluated for inclusion in the PLS model.

MSC treated in-line feed frame spectra of different Ibuprofen blends were plotted in the range of 915-1701 nm. It showed spectral separation in the range of 1100-1701 nm (Fig.4.3c), with notable differentiation around 1100-1250 nm (Fig.4.3d).

For in-line tablet NIRS, spectral range between 1101-1252 nm was selected on the basis of spectral evaluation of earlier off-line tablet NIRS data. MSC treated spectral plot (Fig.4.3e) showed clear spectral differences in 1101-1252 nm range (Fig.4.3e) for NIR spectra of tablets having different Ibuprofen concentrations. Meza et al. [120] reported strong reflectance bands for Ibuprofen in the range of 1122 to 1235 nm which confirmed the present spectral variations as a result of different Ibuprofen concentrations in the blends/tablets.

4.3.6 PCA and PLS analysis

After off-line NIRS and UV testing of tablet sub-samples, the in-line NIRS spectra of feed frame blends and compressed tablets were qualitatively assessed by PCA, followed by quantitative PLS analysis. PCA helped to compare and select different wavelengths and verify if process monitoring was possible in the absence of the quantitative model. PCA score value trends over time were followed for Ibuprofen concentration changes inside the feed frame as well as in tablets. Quantitative analysis of NIR spectra was performed by making PLS calibration models using selected NIR spectra and corresponding concentrations in each data set, later these models were used to predict concentrations in larger data sets as summarized in Table 4.3.

Table 4.3: Summary of different PLS models

NIR spectra	PLS calibration model		Concentration prediction for
	X matrix	Y matrix	X matrix
Off-line tablet testing	Off-line NIR spectra of selected tablet sub-samples (105×283) (105 tablets × 283 wavelengths)	Weight-corrected UV assay values of respective samples (105×1) (105 tablet concentrations)	Off-line NIR spectra of all tablet sub-samples (312×283) (312 tablets × 283 wavelengths)
In-line feed frame monitoring	Selected in-line spectra of stable concentration region (500×26) (100 spectra for each of the 5 concentrations × 26 wavelengths)	Corresponding expected concentration based on average UV assay tablet values (500×1) (100 expected concentration values for each of 5 concentrations)	In-line spectra of all blend samples inside the feed frame (1804×26) (total 1804 in-line NIR spectra × 26 wavelengths)
In-line tablet monitoring	In-line NIR spectra of selected tablet sub-samples (105×50) (105 tablets × 50 wavelengths)	Weight-corrected UV assay values of respective samples (105×1) (105 tablet concentrations)	In-line NIR spectra of all tablet samples (51,459×50) (51459 tablets × 50 wavelengths)

4.3.7 Kinetics

A recent study [20] discussed the kinetics of concentration changes inside the feed frame by describing a continuously-stirred tank. Ibuprofen concentration changes inside the feed frame and tablets were evaluated per first-order rate kinetics, as per equation 4.2:

$$\hat{y} = y_0 + Ae^{-kt} \quad (4.2)$$

where \hat{y} is predicted Ibuprofen concentration inside the feed frame or in tablets, y_0 is Ibuprofen concentration before transition, A is the theoretical value of Ibuprofen concentration difference before and after the transition, k is the first-order rate constant, and t is time in minutes.

PLS predicted concentrations inside the feed frame and in tablets were subjected to first-order curve fitting to evaluate concentration change rate constant k with in-house Matlab scripts (Mathworks, Natick, MA, USA). The time required for each concentration transition inside the feed frame and in tablets was estimated on the basis of respective k values.

4.3.8 Sample volume inside the feed frame

NIR sample volume is an important parameter to study the level of scrutiny in in-line process monitoring since effective sample volume in blend uniformity analysis should be comparable to unit dose [32]. Sample volume was estimated by NIRS sample area/spot size of the NIRS probe, integration time, material bulk density and NIR penetration according to equation 4.3:

$$\text{Sample Volume} = R \times B \times C \quad (4.3)$$

where R is NIRS sample area, B is the NIRS penetration depth, and C is sample bulk density. Inside the feed frame, NIRS sample area was 15×5 mm and integration time for raw spectrum was 5 ms. Each NIR spectrum was obtained by averaging 50 raw spectra acquired in succession. Thus, the total integration time per NIR spectra was 250 ms. Sample area was calculated by considering material movement within this time based on feed frame rpm. NIR penetration depth was considered to be 1.5 mm as reported in an earlier work [110] performed on loose powder material using same NIR probe. Powder sample tested by each NIRS spectrum was compared with equivalent tablet size, considering an average tablet weight of 1200 mg. The total amount of feed frame powder sample tested by NIRS over the entire tablet compression process was compared to total batch size to estimate the level of scrutiny inside the feed frame.

4.4 Results and discussion

4.4.1 Tablet off-line testing

4.4.1.1 UV assay testing of tablet sub-samples

The UV assay results of a few initial tablet samples in 8, 15.8, and 18% w/w Ibuprofen blends indicated lower Ibuprofen contents than the rest of the samples, while the first few tablet samples of 0% w/w Ibuprofen blends showed the presence of Ibuprofen pellets. Temporally stratified tablet samples were collected in 2 different phases, i.e., transition and stable concentration phases, considering that each transition phase would last for the time equivalent to compressing the volume of powder blend comparable to double the feed frame volume. Accordingly, tablet sub-samples were collected from stable-phase tablets and expected to have stable Ibuprofen concentrations, but the UV assay results of initial tablet samples showed that respective transitions were not completed when these tablet samples were collected. Thus, every transition took more than twice the feed frame volume to complete. This observation helped to understand the concentrations transition process inside the feed frame, as explained later in Section 4.4.4. The average Ibuprofen assay values of stable-phase tablets from each blend were considered as assay values of the corresponding blend and later used in the analysis of NIR spectra collected at feed frame and tablet monitoring.

4.4.1.2 NIRS testing of tablet sub-samples

The PLS calibration model was built with the off-line NIR spectra of tablets which showed stable concentrations (105 tablets) in UV testing among the total sub-samples (i.e., 312 tablets). This model served to predict the % w/w of Ibuprofen concentrations in all 312 tablet sub-samples. The PLS calibration model considered off-line NIR spectra as independent variables / X matrix (105×283) and the UV assay values of respective tablet samples as dependent variables / Y matrix (105×1), where 283 points represented wavelengths in the range of 1100-1250 nm, and 105 points represented the number of tablets used in the PLS calibration model.

PLS model-predicted Ibuprofen contents of the tablet sub-samples using different wavelength datasets were compared with UV assay values of the respective tablet samples.

The accuracy of PLS predictions was based on calculated RMSE values between PLS predictions and UV assay values, as depicted in Table 4.4

Table 4.4: RMSE values at selected wavelength ranges

Wavelength range (nm)	RMSE between tablet concentrations by UV assay and off-line NIRS
1100-1250	1.30
1321-1500	4.45
1600-1901	3.77
2101-2701	1.83
1100-2701	2.28
1100-1250, 1321-1500, 1600-1901, 2101-2701	2.00

Among all tested wavelength ranges, the 1321-1500 nm range showed the highest RMSE values while 1100-1250 nm showed the lowest RMSE values, indicating that the PLS model-predicted Ibuprofen content of tablets was close to their Ibuprofen UV assay values. As shown earlier in Figure 4.1, a characteristic Ibuprofen peak is present between 1100-1250 nm. Incorporating multiple wavelength selections in the PLS model improved concentration predictions, but it was still distant from the UV results compared to 1100-1250 nm.

The R^2_{adj} value for the PLS calibration model with 1100-1250 nm spectra using 2 latent variables was 0.96 with RMSEC, and RMSECV (using random-subset cross-validation) values of 1.12 and 1.14 showed that the model fitted well in the selected NIRS spectral range. Comparison of PLS-predicted concentration with the corresponding UV assay results (Fig.4.4) of the tablets demonstrated good agreement between off-line NIRS spectra and the UV assay of tablets.

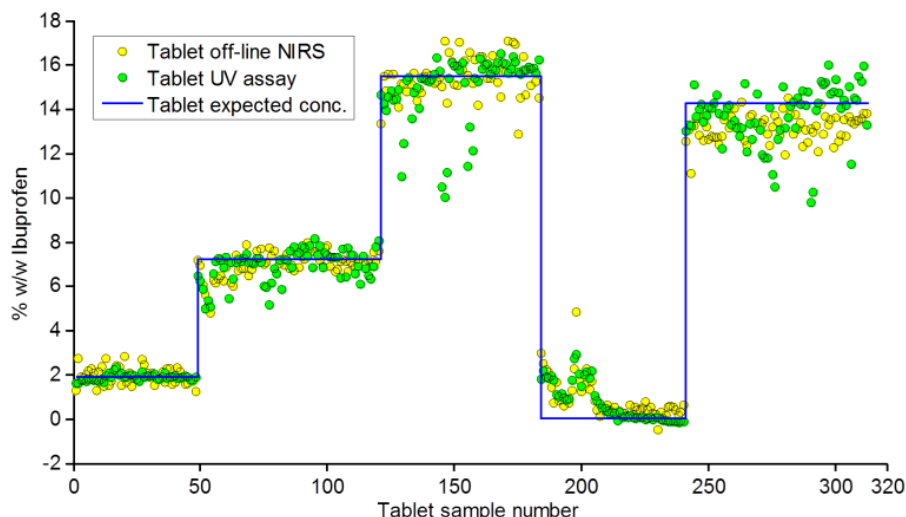


Figure 4.4: Plot of UV assay results versus off-line NIRS-predicted Ibuprofen concentrations in tablet sub-samples

The low RMSE value (1.3% w/w Ibuprofen) in the case of the 1100-1250 nm range showed that NIRS-predicted % w/w Ibuprofen concentration in tablets and actual UV assay values were close in all blends, meaning that NIRS was suitable for Ibuprofen concentration predictions in tablets. The polymer coating on the surface of Ibuprofen pellets did not prevent successful quantification of Ibuprofen by the quantitative model based on NIR spectral data. Few tablets in the 18 and 15.8% w/w Ibuprofen blends had UV assay values lower than the rest of the group, which indicated tablet-to-tablet content variation as well as variation in the surface distribution of Ibuprofen pellets since NIRS PLS predictions of these tablets were close to the rest of the group. A small increase in Ibuprofen contents around the 200th tablet was well matched in both UV assays and NIR PLS predictions, showing true Ibuprofen content change in the tablets. As a result, off-line tablet analysis by NIRS could be a good option for end-product quality control, but it will be time-consuming and practically challenging since every tablet has to be scanned manually. However, in-line NIRS testing of tablets would certainly be beneficial. In-line NIRS data collected inside the feed frame and in tablet monitoring were subjected to qualitative and quantitative analysis to verify NIRS potential for in-line process monitoring.

4.4.2 In-line NIRS qualitative testing inside the feed frame and tablets

In-line NIRS inside the feed frame recorded a total of 1804 spectra over the entire compression run at a rate of 1 spectrum per 4.61 s, while in-line tablet NIRS recorded a total

of 51,459 spectra, one for each tablet. Spectral analysis was preceded by wavelength range and spectral pre-treatment selection.

4.4.2.1 Qualitative testing inside the feed frame

PCA of complete NIR spectra (900-1701 nm) revealed that the 1st and 3rd principal components (PC1 and PC3), which captured 93.57% of total variance, mostly represented baseline variations in NIR spectra. PC1 captured baseline variations at the start and end of the process while PC3, in addition, disclosed baseline variations as a result of material level changes inside the feed frame. PC2 captured 6.09% of total variance, but its score values changed over time according to sequential Ibuprofen concentration changes inside the feed frame. Overall PC score values were higher at the beginning and end of compression with a sharp rise and fall in 2 instances in the middle of the compression process. This is because the feed frame was not completely filled, as NIR acquisition started at the beginning of compression while the feed frame at the end of compression had already commenced emptying when the last few NIR spectra were recorded. Material flow obstruction caused 2 incidents of lower material level inside the feed frame whose time (between 20-30 min and 70-80 min of compression) matched corresponding changes in PC score values. Reflectance NIR spectra plotted over time indicated baseline variations at corresponding time intervals. Thus, PC1 and PC3 were correlated to the spectral baseline variations caused by a material level change inside the feed frame.

This result demonstrated that spectral baseline variations caused by a physical change in the material level were significant and not completely removed by spectral pre-treatment. Including complete spectra in the analysis gave excessive emphasis to spectral changes elicited by factors other than concentration. In contrast, PC1 captured 79.01% of total variance (Fig. 4.5a) and correlated with concentration changes inside the feed frame upon removal of spectra with higher baseline variations from the start and end of the compression process.

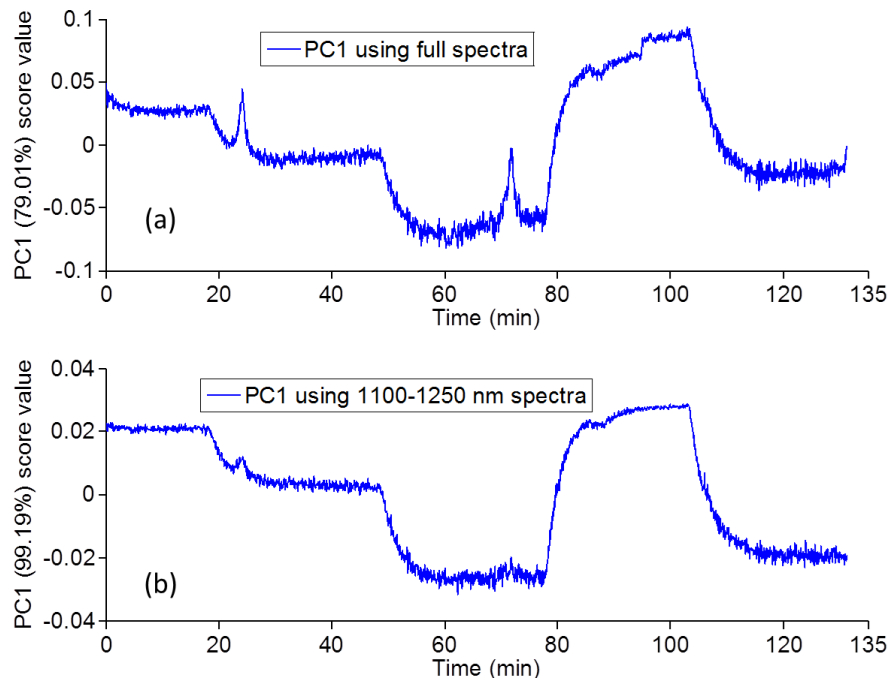


Figure 4.5: (a) Score plot of PC1 for PCA using full NIR spectra (1100-1701 nm). (b) Score plot of PC1 for PCA using selected NIR spectra (1100-1250 nm) inside the feed frame

A second PCA was performed with the same spectral pre-treatment (MSC followed by mean centering) but using selective spectral range, i.e., 1100-1250 nm instead of full spectra. Selected wavelengths shifted the PCA focus from baseline variation to concentration changes inside the feed frame, since this region of NIR spectra represents Ibuprofen specific reflectance peaks. PC1 captured the highest total variance (86.60%) correlated with concentration changes inside the feed frame. PC2 captured the next highest variance (12.30%) correlated with material level changes, while PC3 captured the least variance (0.56%) containing, mainly, information related to baseline variations. Removal of the first and last few acquired spectra (when the feed frame was not completely filled) improved the PCA results, with PC1 capturing 99.19% of total variance (Fig. 4.5b), which clearly correlated with the switch between stable and transition phases of the different blends. PC1 score values also highlighted regions where the feed frame had less material. PCA scores for the 2% w/w blend showed gradual stabilization, indicating that material level inside the feed frame was stabilized after some time. Gradual score value changes on either side of all blend stable phases showed NIRS sensitivity to small traces of Ibuprofen inside the blends.

4.4.2.2 Qualitative testing of tablets

PCA of in-line tablet NIR spectra was performed in the 1101-1252-nm range since it was found to be suitable in off-line NIR testing of the same tablets. PC1 captured 61.53% of total variance (Fig. 4.6) and its values changed over time according to the blend Ibuprofen concentration changes occurring inside the feed frame. PC1 scores of a few tablets showed widely scattered values than the rest of the group, either because of spectral variations resulting from sample presentation to the probe, e.g., spectra taken from partial tablet area or actual concentration variation inside the tablets. Despite variations within the score values of individual tablets, all tablet batches were well distinguishable by the PCA scores.

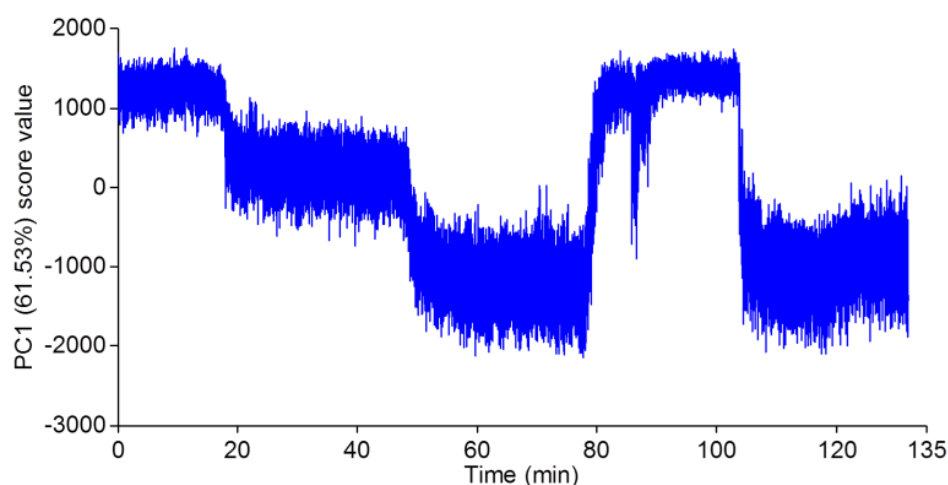


Figure 4.6: PC1 values for all tablets using NIR spectra in the 1101-1250-nm range

4.4.3 In-line NIRS quantitative testing inside the feed frame and in tablets

After wavelength selection and qualitative analysis of in-line NIRS data on the feed frame and tablets, quantitative PLS analysis was performed to acquire actual concentration values of the feed frame blends and tablets.

4.4.3.1 Quantitative analysis inside the feed frame

The PLS calibration model for the feed frame was built with spectra that showed stable PC1 score values among all spectra of respective blends in the 1100-1255-nm spectral range. The model with 2 latent variables showed R^2_{adj} value of 0.995. RMSEC and RMSECV values were 0.46 and 0.47% w/w Ibuprofen, respectively. Considered together, these values show a good fit between the PLS calibration model and the selected NIR spectra. Concentrations for all feed frame NIR spectra were predicted on the basis of this calibration model.

NIRS PLS-predicted Ibuprofen concentrations versus time plots (Fig. 4.7) showed comparatively less scatter around expected concentrations in case of 2, 8 and 0% w/w Ibuprofen blends than in case of 18 and 15.8% w/w Ibuprofen blends. A valley of predicted concentrations (Fig. 4.7) seen during the transition between 2% and 8% blends (between 20 and 30 min) and the stable phase of 18% blends (between 70 and 80 min) matched earlier PCA score plots (Fig. 4.4a) at respective times and showed the sensitivity of chemometric models to changes in material level inside the feed frame. Spectral baseline changes are significant as the material level drops inside the feed frame (i.e. the powder occupies a smaller portion of the volume) and cannot be completely removed by applied spectral pre-treatment. Thus, Ibuprofen concentrations at these points were erroneously predicted to be lower than the actual concentration. The transition between 18 and 0% blends took a longer time. In addition, it showed a small peak in concentration (between 80 and 90 min) during the transition. In this instance, no change in material level was seen during compression. Thus, the peak in Ibuprofen content of powder blend was ascribed to actually higher Ibuprofen content which was also verified in the UV assay results of tablet sub-samples collected at respective time intervals.

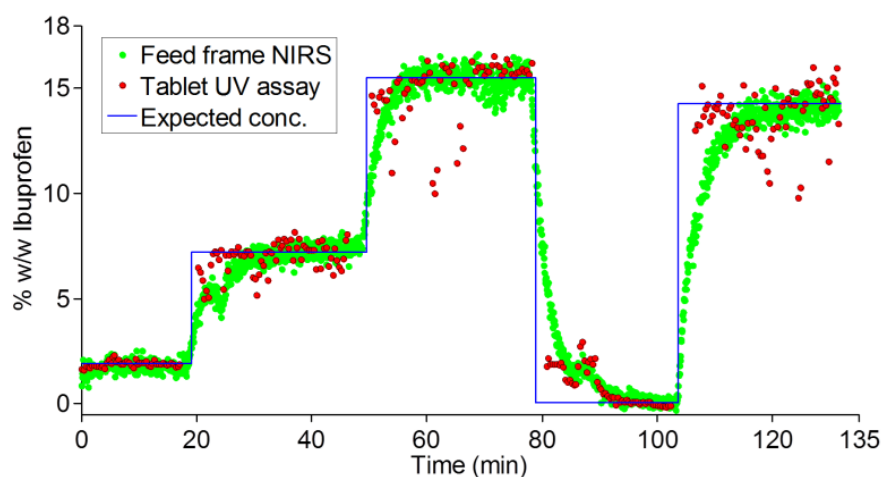


Figure 4.7: NIRS PLS-predicted concentrations inside the feed frame and UV assay of tablet sub-samples

NIRS-predicted concentrations inside the feed frame and the Ibuprofen UV assay results of tablet sub-samples collected at corresponding times showed good agreement. A small increase in Ibuprofen concentration between 18 and 0% transition was equally detected inside the feed frame and by UV. This could be due to some leftover quantity of 18% w/w Ibuprofen

blend being released in main material flow from the hopper. The UV results indicate that the change in concentration was about 1% w/w, which suggests that NIRS can detect small concentration variations inside the feed frame.

4.4.3.2 Quantitative tablet testing

The PLS calibration model was built with the UV assay results of 312 tablet sub-samples and the corresponding in-line NIR spectra of tablets. R^2_{adj} value of 0.92 showed good agreement between the model and the tablets' in-line NIRS data. RMSEC and RMSECV values were 1.83 and 1.87% w/w Ibuprofen, respectively. Adding more than 2 latent variables improved model fit to the data (increased R^2_{adj} and decreased RMSEC as well as RMSECV) but did not show any improvement in concentration prediction (based on RMSEP values). Therefore, only 2 latent variables were selected in the PLS calibration model. Ibuprofen concentration in all tablets (51,459) was predicted on the basis of this calibration model.

Machine-operating parameters suggested that 28 tablets were manufactured between 2 NIR spectra recorded inside the feed frame, as a result for comparison with NIR-predicted Ibuprofen concentration changes inside the feed frame over time; an average concentration of 28 consecutive tablets was used.

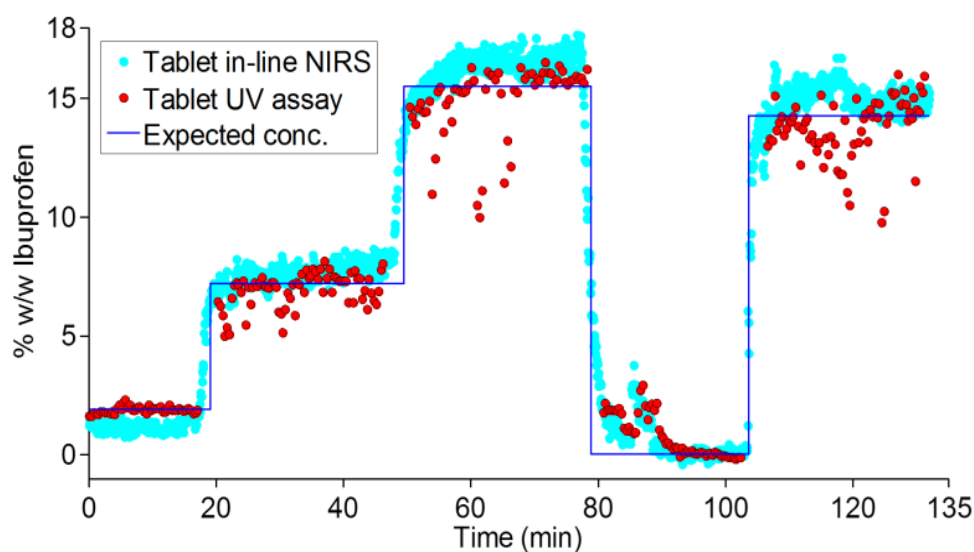


Figure 4.8: NIRS PLS-predicted Ibuprofen concentrations in tablets (average of 28) and UV assay values (no averaging was performed) of tablet sub-samples

The Ibuprofen UV assay results of the tablet sub-samples showed fairly good agreement with the average Ibuprofen concentrations of 28 tablets over time when plotted together (Fig. 4.8). However, the un-averaged NIRS PLS-predicted Ibuprofen concentrations of all tablets

(51,459) showed higher tablet –to– tablet variation similar to the variation shown by certain tablets in UV assay. The variation within NIRS results could be due to the difference in the surface distribution of Ibuprofen pellets, actual content variation (as indicated by UV assay of few samples) and spectral variations as a result of dynamic sample presentation.

The predicted % w/w Ibuprofen concentrations of 379 out of 51,459 tablets tested were far lower or higher than the average predicted concentrations of respective blends (beyond 2σ) and are considered outliers. It is very likely that these samples were not well positioned with respect to the NIR probe illumination spot, resulting in NIR spectra recorded from partial tablet area. The NIR spectra of these tablets were removed from further testing.

A small peak in predicted concentration during transition of 18 % to 0 % w/w Ibuprofen blends matched well in NIR PLS-predicted Ibuprofen in tablets and UV assay results of tablets sub-samples collected at respective time confirming that Ibuprofen concentration change was result of actual change in powder blend and not due to physical phenomenon affecting NIR spectra e.g. as low material level inside the feed frame.

4.4.3.3 Comparison of off-line and in-line PLS in tablet monitoring

Plotting predicted tablet concentrations (312 tablets sub-samples) with off-line and in-line NIRS PLS models (Fig. 4.9) showed prediction accuracy of the respective PLS model.

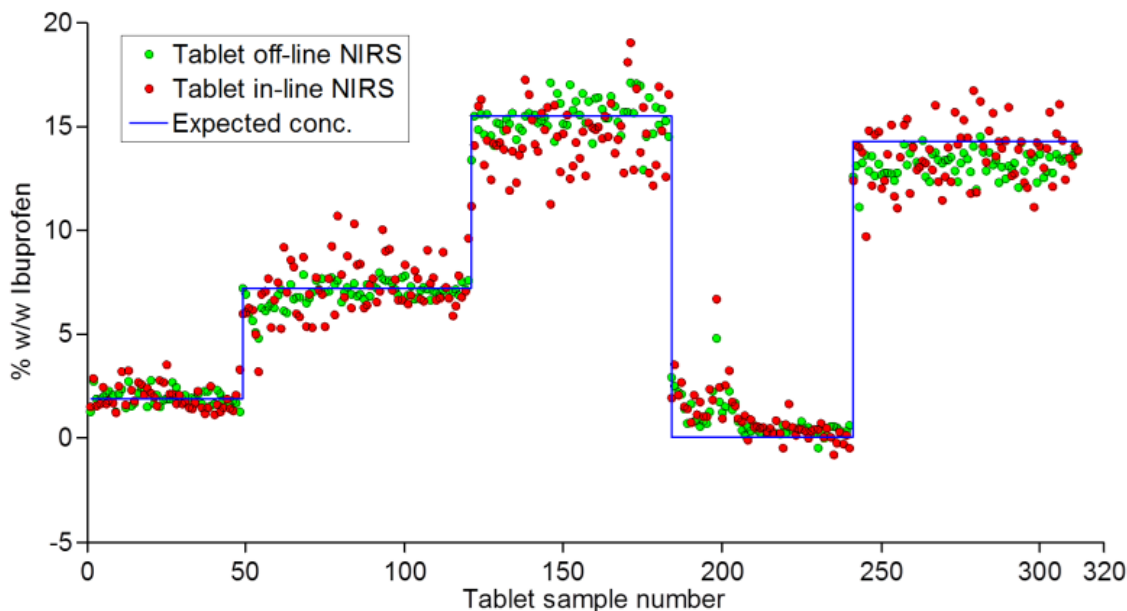


Figure 4.9: PLS-predicted tablet concentrations with off-line and in-line NIRS

Ibuprofen concentration in tablets predicted by off-line NIRS was more closely spread near expected values than in-line NIRS. The RMSE value between the UV assay results and off-line NIRS-predicted concentrations was 1.30% w/w while RMSE between the UV assay results and in-line NIRS-predicted concentrations was 2.31% w/w, which shows that in-line NIRS-predicted concentrations are slightly over or under estimated than the actual UV assay values. The spread of individual tablet concentrations was quantified with standard deviations in all stationary phase tablets at each concentration (Table 4.5). While standard deviation of off-line NIRS closely matched the UV assay results, the standard deviation of in-line NIRS concentrations was higher than the respective values of off-line NIRS and UV assay. Since the same tablet samples were tested by all 3 methods (UV assay, in-line and off-line NIRS), standard deviation values indicated that factors, such as dynamic sample presentation and lesser spectral integration time in case of in-line analysis, led to slightly higher tablet-to-tablet variation in predicted % w/w Ibuprofen concentrations of the tablets.

Table 4.5: Standard deviation of tablet concentrations by NIRS and UV assay

Tablet sub-sample testing method	Standard deviation value for tablets with different % w/w Ibuprofen contents				
	0 % w/w	2 % w/w	8 % w/w	15.8 % w/w	18 % w/w
UV analysis	0.88	0.14	0.71	1.28	1.52
Off-line NIRS	0.89	0.39	0.59	0.60	0.86
In-line NIRS	1.21	0.61	1.35	1.40	1.59

4.4.4 In-line concentration change kinetics

Concentration step changes of NIRS-predicted Ibuprofen concentrations inside the feed frame and tablets were found to obey first-order kinetics (2). The first-order rate constant (k) and its 95% confidence interval were calculated after curve-fitting (Tables 4.6 and 4.7).

4.4.4.1 Kinetics inside the feed frame

First-order kinetic rate values k for different transitions are found in Table 4.6.

Table 4.6: Kinetics of blend concentrations inside the feed frame

Blend transition	First-order rate constant (k) (min^{-1})	95 % Confidence interval (min^{-1})	Time required for 75 % transition (min)
2-8 % w/w	0.196	0.185-0.206	7.098
8-18 % w/w	0.359	0.350-0.369	3.878
18-0 % w/w	0.352	0.343-0.361	3.951
0-15.8 % w/w	0.280	0.276-0.284	4.976

The time required to achieve 75% of blend transitions (calculated from first-order rate equation (4.2)) inside the feed frame was observed to be different for all blends, leading to the conclusion that each incoming blend from the hopper does not follow the same kinetics inside the feed frame, despite having similar qualitative composition and constant compression machine settings. In a completely-filled feed frame, only a small portion of the total material present inside the feed frame enters the dies during each paddle wheel rotation. At a constant tableting rate and constant speed of the feed frame paddle wheel, a fixed amount of material was removed from the feed frame while the rest was circulated back to it. Material entering the dies could not be controlled selectively. Thus, the incoming material randomly mixes with the material already present inside the feed frame before replacing it completely. This could have led to random variation in first-order rate constants. Random mixing is more explicit at the second wheel due to the design of the feed frame as explained in the following section (3.4.2). In addition, blend flowability might impact the concentration change kinetics. However, in the present work, the flowability of all blends was considered to be the same and not tested separately owing to the fact that mannitol compensates for the major portion of the change in Ibuprofen pellet concentration, and its particle size is close to that of Ibuprofen pellets.

4.4.4.2 Kinetics in tablets

To evaluate tablet and feed frame concentration changes on the same time scale, concentration kinetics inside the tablets were found from the predicted Ibuprofen

concentrations averaged over 28 tablets. The rate constant (k) values, confidence interval and time required for 75% completion of different transitions are summarized in Table 4.7.

Table 4.7: Kinetics of blend concentrations in tablets

Blend transition	First-order rate constant (k) (min^{-1})	95 % Confidence interval (min^{-1})	Time required for 75 % transition (min)
2-8 % w/w	1.062	0.947-1.177	1.317
8-18 % w/w	0.501	0.481-0.522	2.780
18-0 % w/w	0.712	0.673-0.752	1.976
0-15.8 % w/w	1.220	1.124-1.315	1.171

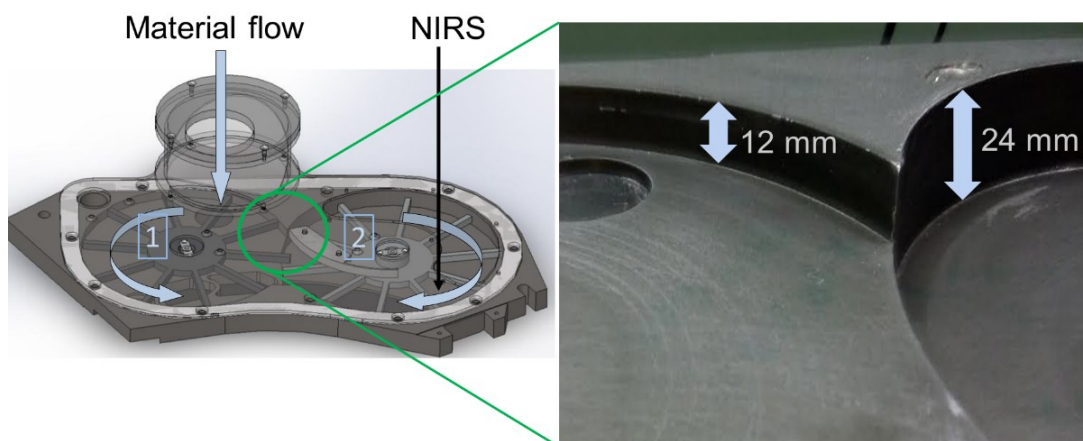


Figure 4.10: Differences in feed frame depth at the first and second wheel

The time required for 75% completion of concentration transitions in case of tablets did not show similar trends as the feed frame. Overall kinetics within the tablets appeared to be faster than in the feed frame. This could be due to the positioning of NIRS on the feed frame. The NIR probe was located at the second wheel (Fig. 4.10) while die-filling started from the first wheel. Most of the tablet mass was taken from the first wheel since empty dies first passed under the first wheel. In addition, feed frame depth was 12 mm at the first wheel and 24 mm at the second wheel. The height of the individual paddles was 7.5 mm. Thus, the material had less space to escape the first wheel and was carried along the paddles. As a result, the existing material at the first wheel either filled the dies or was pushed on to the second wheel under paddle motion as well as pressure from the hopper material. Thus, it was likely

that the first wheel equilibrated faster with the incoming material than the second wheel where the material was removed comparatively slower by dilution with incoming material.

4.4.4.3 Comparison of kinetics inside the feed frame and inside the tablets

The plot of Ibuprofen concentration changes versus time (Fig. 4.11) inside the feed frame and tablets showed that transition started slightly earlier in the tablets than in the feed frame. In addition, it took a little longer for completion inside the feed frame than in the tablets. NIR probe position should be optimized to observe concentration changes simultaneously with tablets since die-filling starts at the first wheel and the NIR probe is positioned at the second wheel.

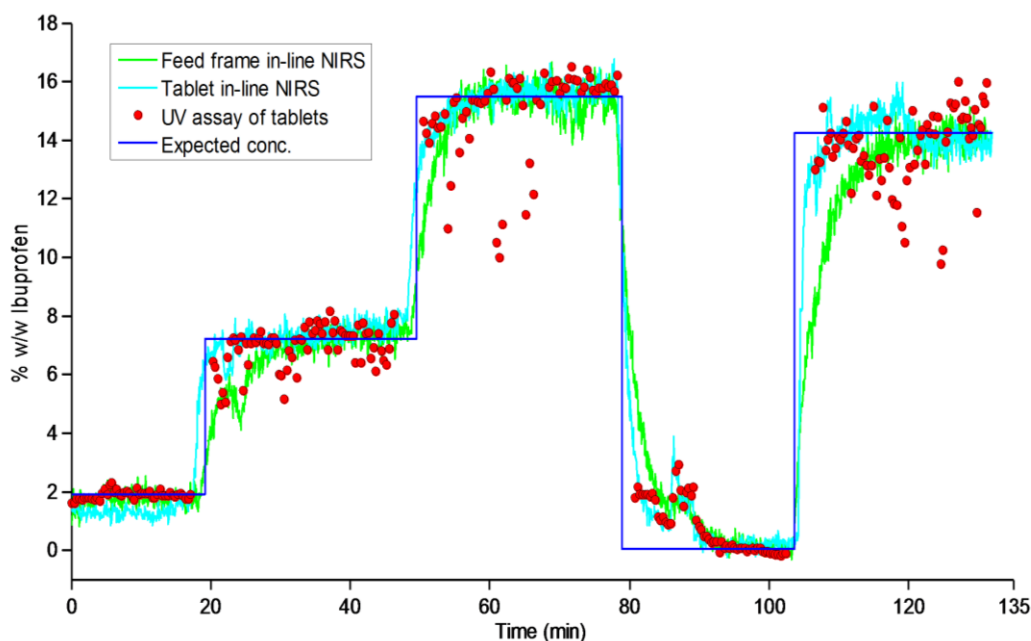


Figure 4.11: Ibuprofen concentration comparison inside the feed frame and tablets with expected concentration as well as UV assay values of tablet sub-samples

4.4.5 Sample volume inside the feed frame

Sample volume per NIR spectrum was determined to be 299.6 mg/spectrum (equation 4.3). Thus, each spectrum represented about 0.25 dosage units. Considering the total number of spectra (1804) recorded throughout compression, the total sample tested by NIRS inside the feed frame was estimated to be 540.5 g, which represents 0.72% of the total batch size. The present study recorded only one NIR spectrum per revolution of the feed frame paddle wheel. The percentage of the total tested sample could be improved by increasing the frequency of

NIRS data acquisition. Sample volume per spectrum could be augmented by increasing integration time and averaging a large number of sub-spectra since powder blends inside the feed frame are moving continuously. However, the possibility of losing local variations as a result of excessive averaging should also be tested.

4.5 Conclusion

The present work sought to evaluate the feasibility of near-infrared spectroscopy (NIRS) to monitor concentrations in a pharmaceutical tableting. The novelty of the work lies in the fact that 3 NIRS systems were used to monitor different aspects of the compression process: 1) in-line analysis of flowing powders inside the feed frame, 2) in-line analysis of all tablets produced and 3) off-line analysis of a sub-sample of the tablets. To achieve this, Ibuprofen was used as an Active Pharmaceutical Ingredient (API) in concentrations between 0 and 15.3 % w/w.

NIRS responses to subtle concentration changes inside a feed frame and in the tablets during the compression process were evaluated through a series of controlled concentration step changes inside the press hopper. Multivariate partial least-squares (PLS) models were used to predict Ibuprofen concentrations inside the feed frame and tablets. These models were compared to UV assays of the tablets collected at different time points during compression. Process kinetics, in terms of the rate with which Ibuprofen concentrations would change in the flowing powder as well as in the tablets, were measured and compared.

Results highlight the feasibility of NIRS to accommodate different physical sample presentations, i.e. powders and tablets. A concentration difference as low as 1.7% w/w Ibuprofen was successfully detected despite Ibuprofen being present in coated particulate form and sample spectra being acquired in dynamic mode. Good agreement between NIRS-PLS model predicted concentrations inside the feed frame and tablets with the UV assay results substantiated the potential NIRS for feed frame- and tablet-monitoring.

Ibuprofen concentration changes, both in the feed frame and in the tablets, could be modeled using first-order kinetics. However, a difference of about 1.25 min was observed, tablets show transition onset 1.25 min ahead of the feed frame. This result indicates that NIR probe position inside the feed frame must be chosen based on the geometry of feed frame to better correlate with the concurrent tablet concentration dynamics or a delay to see

concentration change inside feed frame based on its location inside feed frame should be established case by case. NIRS also showed sensitivity not only for concentration changes but also for level changes inside the feed frame (i.e. void space), which could potentially be useful when seeking to control a commercial press. Finally, a combined feed frame and tablet monitoring could prove beneficial in the real-time release testing of batches.

Acknowledgments

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CHAPTER 5 In-line concentration monitoring in a multicomponent blend inside the tablet press using NIR CI (area scan)

Titre en Français:

Suivi en ligne de la concentration d'un mélange multi composite par NIR CI lors de la compression

Summary

Contents:

NIR CI (area scan) has been successfully used to qualitatively and quantitatively differentiate different blends according to Ascorbic acid concentration in the blends (chapter 3) in off-line tests. The composition of the powder blends was comparatively simple since it only contained 3 ingredients. However, average pharmaceutical tablet composition contains multiple ingredients; thus it is necessary to evaluate NIR CI for concentration monitoring in complex pharmaceutical blends. This chapter shows the in-line performance of NIR CI (area scan) for Ibuprofen concentration monitoring in a pharmaceutically relevant complex blend composition containing multiple non-active ingredients.

Results:

NIR CI (area scan) based PLS models suitably predicted Ibuprofen concentration changes. However, the signal-to-noise ratio for concentration predictions in respective blends was found lower than NIRS. The accuracy of NIR CI (area scan) data was negatively influenced by the presence of multiple pharmaceutical ingredients in the powder blend.

Contributions to the thesis:

Evaluation of NIR CI (area scan) for powder concentration prediction in a pharmaceutically relevant blend composition was demonstrated. Higher noise in NIR CI (area scan) data suggests that the complex nature of the powder blend poses a challenge for the NIR CI (area scan) data accuracy. This chapter suggests that NIR CI (area scan) could be suitable for feed frame monitoring if the signal-to-noise ratio in data collection is improved. One way of achieving this could be- to use a spectrograph in front of NIR camera (i.e. line scan) which would help to obtain spectral data with a precision close to NIRS (chapter 6).

Abstract

NIR CI (area scan) has been reported for in-line concentration monitoring inside a tablet feed frame using simple powder blends. In addition to quantitative concentration predictions, NIR CI (area scan) provides the possibility for qualitative process control in the event of material depletion, obstruction of material flow or segregation of powders inside the feed frame. Selectivity of NIR spectral filters can be challenged in the presence of multiple ingredients having NIR absorbance in the similar wavelength range, negatively affecting the concentration prediction by NIR CI (area scan).

The present work evaluates Ibuprofen concentration monitoring in a pharmaceutically relevant multi-component blend using NIR CI (area scan). Predictive models were built using Partial Least Square (PLS) analysis. Concentration predictions inside the feed frame were compared with corresponding NIRS-based concentration prediction inside the feed frame as well as UV assay results of the tablet samples.

Captured NIR CI (area scan) visually demonstrates the difference between the powder blends at different levels of Ibuprofen in their composition. NIR CI (area scan) PLS model predicted concentrations show that the broad changes in Ibuprofen concentration are successfully monitored by NIR CI (area scan) despite the presence of other multiple ingredients. Compared to NIRS PLS concentration predictions inside the feed frame and UV spectroscopic assay analysis, NIR CI (area scan)-based concentration predictions show a higher sample-to-sample variation which is due to lower signal-to-noise ratio in NIR CI (area scan) data.

Keywords: NIRS; NIR CI (area scan); tablet; feed frame; segregation

Résumé français:

La NIR CI (area scan) est utilisée pour le contrôle en ligne d'une concentration dans des mélanges simples de poudres, dans une trémie d'alimentation de presse à comprimée. Outre des prévisions de données quantitatives, la NIR CI (area scan) offre la possibilité d'un contrôle qualitatif du procédé en cas d'épuisement de la matière, d'obstruction du flux de poudre ou de mélange des poudres à l'intérieur de la trémie d'alimentation. La sélectivité des filtres spectraux NIR peut être remise en question en présence de multiples ingrédients ayant une absorbance NIR dans une gamme de longueurs d'onde similaire, interférant avec la prédiction de la concentration par NIR CI (area scan).

Le travail actuel estime la concentration d'ibuprofène dans un mélange pharmaceutique multi-composant approprié, en utilisant NIR CI (area scan). Les modèles prédictifs sont construits en utilisant l'analyse des Moindres Carrés Partiels (PLS). Les prévisions de concentration à l'intérieur de la trémie d'alimentation sont comparées avec celles basées sur la NIRS dans la trémie d'alimentation ainsi que les résultats d'analyse UV des échantillons de comprimés.

La NIR CI (area scan) permet de démontrer visuellement la différence entre les mélanges de poudre à différentes concentrations en ibuprofène. Les concentrations prédites par le modèle NIR CI (area scan) PLS montre que les importants changements de concentration en ibuprofène sont contrôlés avec succès par la NIR CI (area scan), malgré la présence de multiples autres ingrédients. Comparées aux prévisions de concentration obtenues par NIRS PLS et par analyse par spectroscopie UV à l'intérieur de la trémie d'alimentation, les prévisions de concentration basées sur la NIR CI (area scan) montrent une variabilité inter-échantillon plus élevée, dû à un rapport signal sur bruit plus faible dans les données NIR CI (area scan).

Mots-clés:

NIRS; NIR CI (global); comprimé; plateau d'alimentation; ségrégation

5.1 Introduction

5.1.1 NIR CI in feed frame monitoring

NIR CI-based PAT applications searching for distributions of the active pharmaceutical ingredient in a tablet formulation [121], finding spatially resolved hardness maps across the surface of tablets [122] as well as in determining blending operation end point [38] have already been explored. Powder compositions in these studies were complex and pharmaceutically relevant; however sample data acquisition conditions were comparatively more stable, e.g. tablets were scanned in single unit format by manually placing them under imaging unit while in case of blending end points determination, the blender was stopped when NIR images were acquired. Contrary to most pharmaceutical operations involve moving samples which pose a challenge in NIR CI applications measuring the powder samples in-line. The quality of NIR CI data may be compromised in in-line measurements due to lower signal-to-noise ratio as compared to measurements in stationary samples. NIR CI (global) using a wavelength bandpass filters [123] has been already reported in chapter 3 for feed frame concentration monitoring owing to both spectral and spatial information which could detect adverse quality phenomenon like segregation. An earlier study [124] also shows detection of ingredients in tablet samples using NIR CI. Chapter 3 demonstrated the NIR CI (global) application in feed frame monitoring testing the moving powder samples; however powder samples used therein were less complex in terms of composition. In this regard, it is necessary to evaluate NIR CI (global) for monitoring pharmaceutically relevant compositions containing active of interest along with other pharmaceutically accepted components.

5.2 Materials

Materials, formulation composition, sample preparation and tablet compression sequence used in this work are same as chapter 4.

5.3 Methods

NIR camera was used with a single bandpass filter (discussed below) suitable for capturing Ibuprofen in the presence of other ingredients of the blend composition. Feed frame set up was similar to chapter 3; however, measurements were made in an in-line manner.

5.3.1 Selection of suitable bandpass NIR filter

Different NIR filters were evaluated to obtain NIR (area scan) images showing the proper contrast in image pixels representing NIR absorbing and non-absorbing materials within the NIR wavelength range permitted by the bandpass filter. The NIR camera records images capturing reflected NIR light from the sample surface, consequently, image pixels representing NIR absorbing materials appear darker while pixels representing non absorbing materials appear brighter on the recorded NIR image.

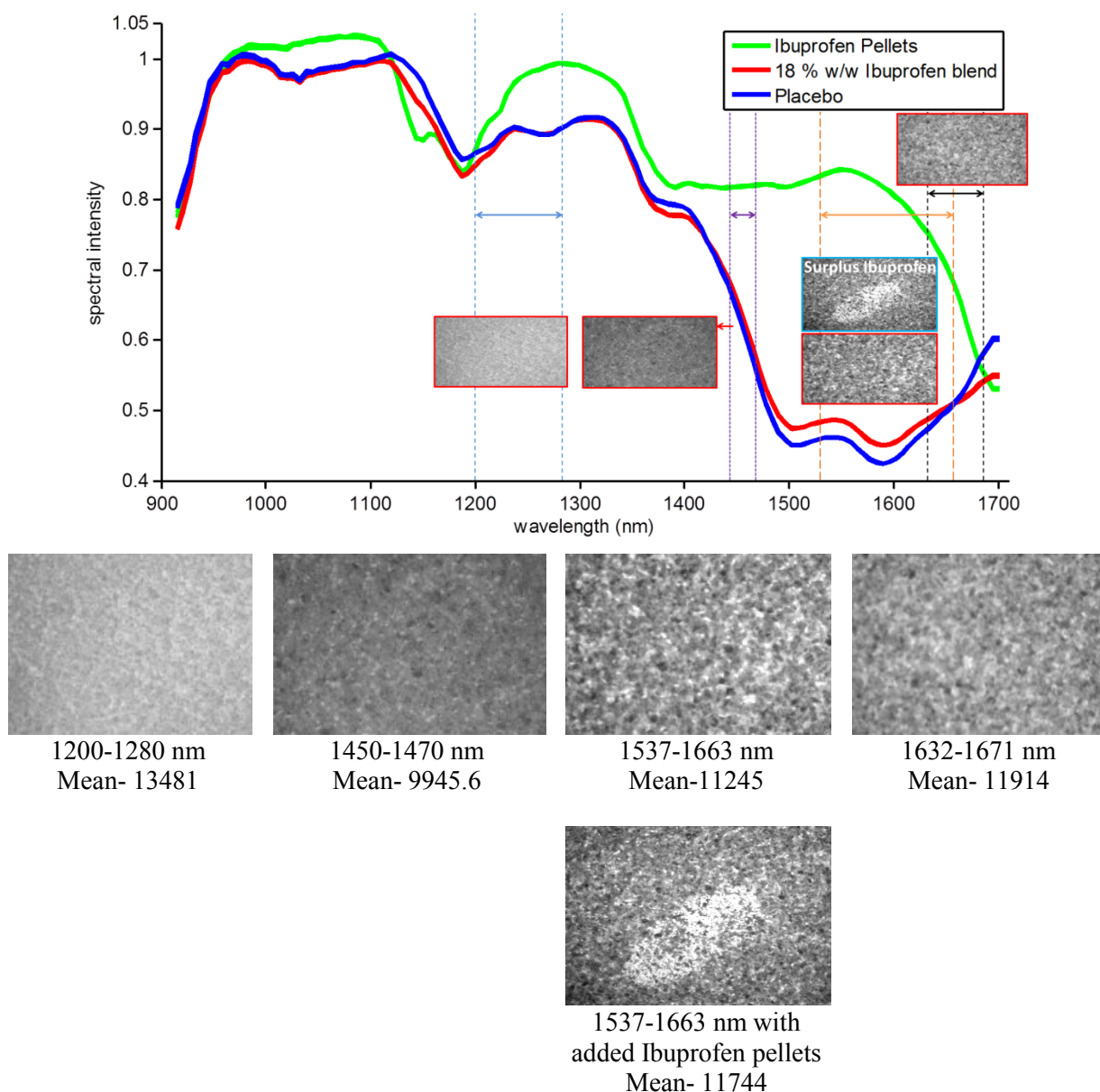


Figure 5.1: NIR CI (area scan) of 18% w/w Ibuprofen powder blends taken with different bandpass filters

Figure 5.1 shows NIR CI (area scan) of 18% Ibuprofen blend captured with different filters. In the present work, Ibuprofen is the active of interest upon which filter selection is dependent, i.e. if Ibuprofen shows NIR absorbance with certain wavelength filter then other ingredients of the powder composition should not absorb NIR radiation in the same wavelength range and vice versa; in order to provide useful pixel contrast in the captured NIR CI (area scan) leading to higher signal-to-noise ratio.

Reflectance spectra of Ibuprofen pellets (Figure 5.1) do not show significant NIR absorption peaks in the range of 900-1600 nm except for 2 small absorption peaks between the ranges of 1150-1250 nm. NIR absorbance increases beyond 1600 nm. In comparison to NIR reflectance spectrum of Ibuprofen pellets, 1200-1280 nm filter represent the spectral region of least NIR absorbance while 1450-1470 and 1537-1663 nm filters cover slightly higher NIR absorbance region of Ibuprofen pellets. However, NIR absorbance of other components (table 4.1) of the blend, also plays a significant role in the NIR CI (area scan) pixel contrast differentiating among different ingredients. Other components of the powder blends show similar absorption peak near 1150-1250 nm while NIR absorbance goes on increasing beyond 1350 nm until 1600 nm. Consequently, NIR CI (area scan) using 1200-1280 nm bandpass filter does not show any pixel contrast for Ibuprofen since neither Ibuprofen nor other blend ingredients significantly absorb in that range, as well as the difference in their NIR absorbance is not greatly different.

However, NIR CI (area scan) with 1537-1663 nm filter showed Ibuprofen as comparatively brighter pixels which were later confirmed by adding an additional quantity of Ibuprofen pellets in the blend. NIR image pixels corresponding to the location of the other components appear darker (i.e. lower pixel intensity than Ibuprofen) in these images, which indicate that other ingredients of the composition absorb more than Ibuprofen in 1537-1663 nm range. Thus the wide gap between their NIR absorbance helps to achieve better pixel contrast for NIR (area scan) using 1537-1663 nm filter. NIR CI (area scan) with 1632-1671 nm filter show low contrast in pixel intensities since Ibuprofen pellets starts absorbing beyond 1650 nm thus reducing the difference in the NIR absorbance of Ibuprofen pellets and other components of the powder blend.

5.3.2 Data Acquisition

Sample presentation to the camera was properly controlled using flat insert (Figure 3.3) to ensure image-to-image comparability. Sample-to-camera distance, optics, illumination and sample surface settings were kept constant. In addition, all NIR images were corrected for NIR source intensity variation over time using a white reference. For this purpose, a white reference was placed next to the flat insert. A ratio between the mean intensity of all the pixels representing this white reference in the respective image and the first image was used to correct the respective image for variation in the NIR light intensity. This ratio was multiplied to all pixel intensities in the NIR chemical image being corrected.

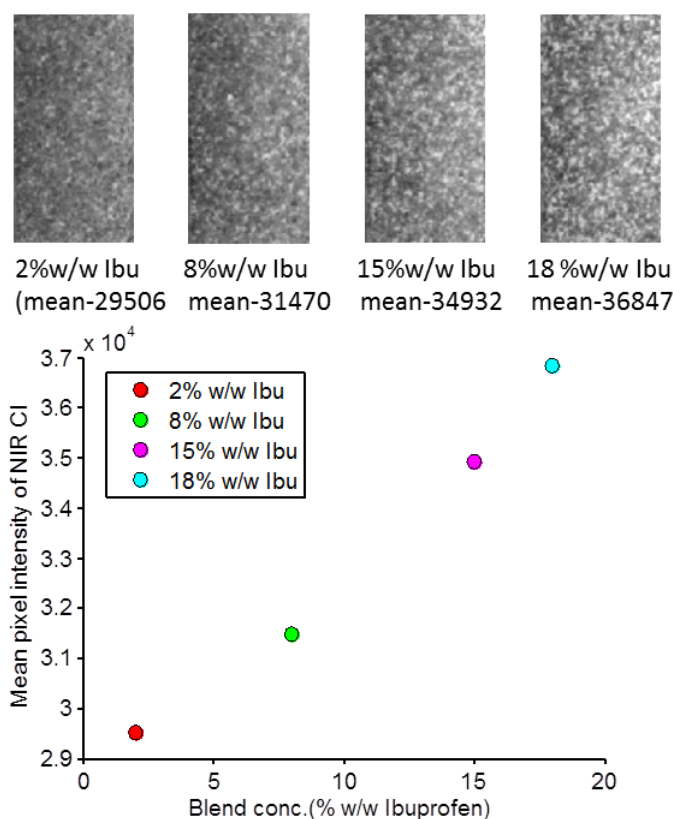


Figure 5.2: NIR CI (area scan) showing different pixel intensities as a function of different Ibuprofen concentration

Figure 5.2 shows a clear difference in the pixel intensities of NIR CI (area scan) taken during the compression of different powder blends with varying Ibuprofen concentration. As the concentration of Ibuprofen pellets increases in the blend, density of brighter pixels in the NIR CI (area scan) increases. Thus, at 2% w/w Ibuprofen concentration NIR CI (area scan) exhibit

lowest mean pixel value, which goes on increasing with increasing Ibuprofen concentration in the blend and reaches to highest for 18 % w/w Ibuprofen blend.

The trend in the mean pixel intensities indicate that selected NIR filter appropriately differentiates the NIR image pixel intensities as a function of Ibuprofen concentration. NIR image pixels distribution according to their intensity can allow comparison between NIR images taken for different Ibuprofen concentration blends. Thus, NIR CI (area scan) can be used for the purpose of Ibuprofen powder blend monitoring.

5.3.3 Data treatment and analysis

NIR CI (area scan) data was analyzed following a similar method of analysis as explained in section 3.4.3 of chapter 3. Initially, histogram analysis was performed following which quantitative analysis was performed using PLS models. Scaling to unit variance and mean centering was used in the data pre-treatment.

5.4 Results and discussion

5.4.1 Comparison of NIR CI (area scan) and NIRS PLS models

The NIR CI (area scan)-based PLS calibration model for the feed frame was built with NIR CI (area scan) data collected during stable concentration phase of different blends. Stable concentration region for each powder blend was selected based on corresponding NIRS spectra (1100-1255nm spectral range) that showed stable PC1 score values (Figure 4.5) in each blend. PLS model with 4 latent variables showed R^2_{adj} value of 0.96. RMSEC and RMSECV values were 1.33 and 1.49 % w/w Ibuprofen, respectively. Calibration model parameters were found inferior to the NIRS data (R^2_{adj} value of 0.995. RMSEC and RMSECV values were 0.46 and 0.47% w/w Ibuprofen with 2 latent variables). Concentrations for all the blends inside feed frame were predicted on the basis of this calibration model.

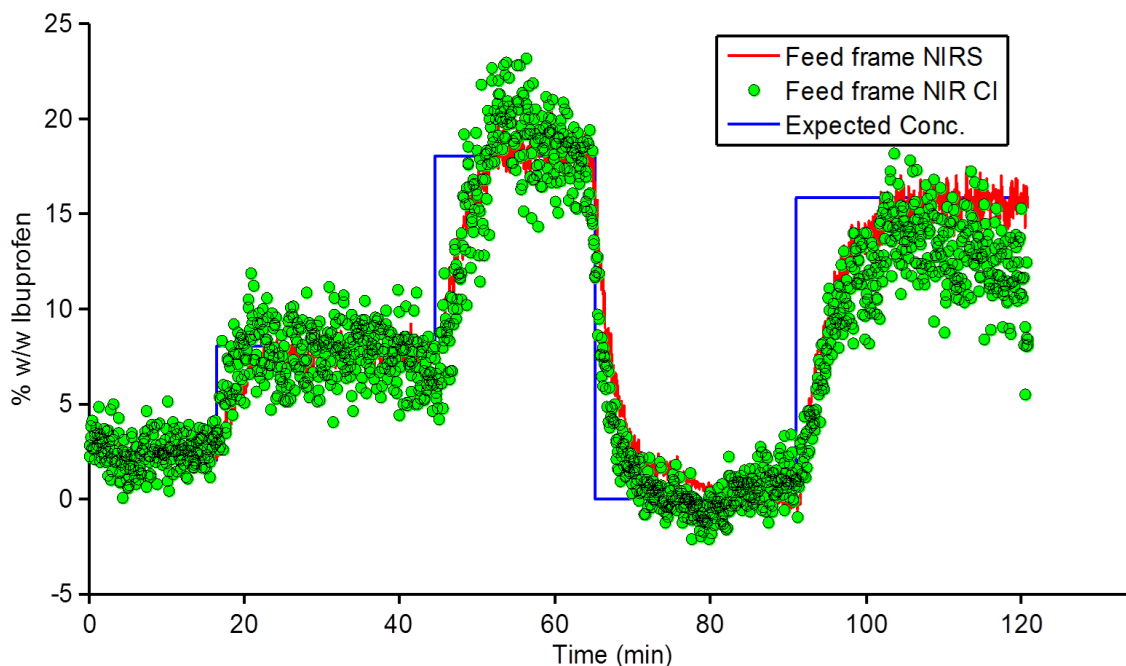


Figure 5.3: NIR CI (area scan) predicted Ibuprofen concentrations inside the feed frame, the expected and NIRS predicted concentrations

NIR CI (area scan) PLS-predicted Ibuprofen concentrations versus time plot (Figure 5.3) show that NIR CI clearly depicted the concentration step changes inside the feed frame. Root mean square error (RMSE) value between NIR CI (area scan) predicted concentration and expected concentration was found 2.98 while a RMSE value between NIRS predicted concentration and expected concentration is 2.34, which indicate NIR CI (area scan) PLS model based concentration predictions are not as close to expected concentration as NIRS. The RMSE between NIR CI (area scan) and NIRS predictions was found as 2.12, which also shows that there is a similar level of difference in NIR CI (area scan) and NIRS predicted concentrations.

NIR CI (area scan) predicted concentrations show higher scatter around expected concentrations upon visual observation of Figure 5.3. The scatter of predicted concentrations was also higher than NIRS predicted concentrations for all the powder blends. The mean and standard deviation of predicted concentration during the steady state of compression were compared with NIRS-based predictions for statistical comparisons.

Table 8: Mean and standard deviation of NIR CI (area scan) and NIRS model predicted concentrations

Expected concentration (% w/w)	NIR CI (area scan) Mean concentration (% w/w)	NIR CI (area scan) standard deviation (% w/w)	NIRS Mean concentration (% w/w)	NIRS standard deviation (% w/w)
0	0.76	0.92	-0.13	0.20
2	2.46	0.93	2.35	0.26
8	7.73	1.39	7.65	0.49
15.8	12.96	1.88	15.42	0.79
18	18.61	1.86	18.26	0.82

As shown in table 5.1, NIR CI (area scan)-based mean concentration predictions for 8 and 15.8 % Ibuprofen blends was slightly lower than expected concentrations while predicted mean concentrations for 0, 2, and 18 % Ibuprofen blends were slightly above the expected concentrations. NIRS PLS model predicted concentrations for 0, 8, and 15.8 % Ibuprofen were slightly lower than expected concentrations while predicted concentrations in the case of 2 and 18 % Ibuprofen were slightly higher than the expected concentrations. In all cases NIR CI (area scan)-based concentration predictions showed higher standard deviation than NIRS-based concentration predictions, indicating higher sample to sample variation in NIR CI (area scan).

Variance calculated for the steady states in the PLS model predicted concentrations (Figure 5.4) increased with increasing blend concentration in both the NIRS and NIR CI (area scan)-based concentration monitoring. However, variance values in NIR CI (area scan) predicted concentrations at all blend concentrations were higher than NIRS, indicating that signal-to-noise ratio in case of NIR CI (area scan) is slightly lower than NIRS.

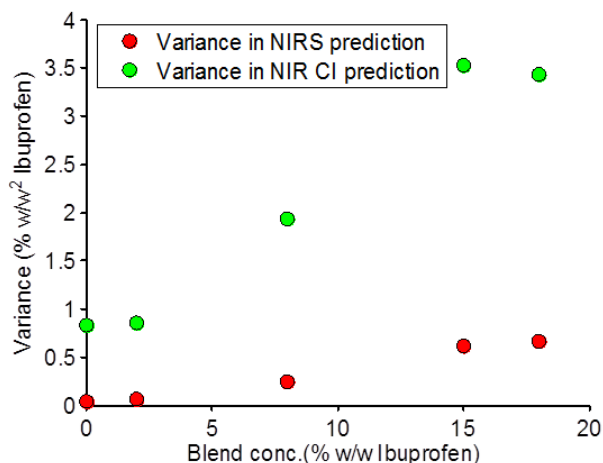


Figure 5.4: Variance in NIRS and NIR CI (area scan) predicted Ibuprofen concentrations inside the feed frame

5.4.2 Comparison of NIR CI (area scan) predicted concentrations with tablet assay

Powder concentration predictions using the PAT tools need to be verified against routine chemical analysis methods to avoid misleading conclusions on the product/process quality just based on chemometric model performances. Thus, NIR CI (area scan)-predicted concentrations inside the feed frame and the Ibuprofen UV assay results of tablet sub-samples collected at corresponding times were compared (Figure 5.5). Gross changes in powder blend concentrations inside the feed frame are clearly captured by NIR CI (area scan) predicted concentrations; however, NIR CI (area scan) predicted sample-to-sample concentrations among the respective blends vary considerably in comparison to UV assays of the tablet samples. As discussed in chapter 4, UV assay of certain tablets in the 15.8 and 18 % blend were scattered from rest of the tablets, however, scatters in the corresponding NIR CI (area scan) predicted concentrations were seen even higher. This indicates the presence of variation/noise in the gathered NIR CI (area scan) data in addition to the original level of concentration variations seen in the blend compositions owing to UV spectroscopic assays.

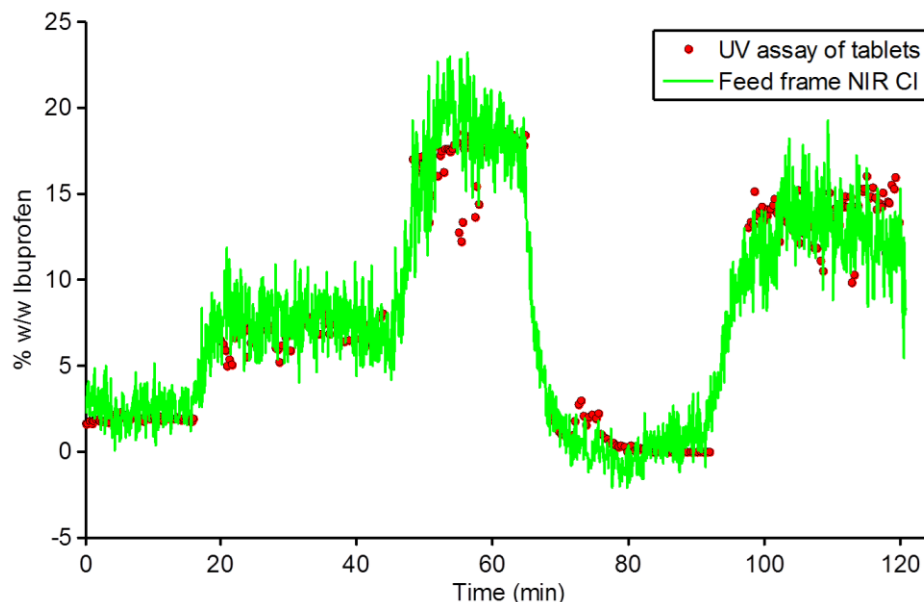


Figure 5.5: NIR CI (area scan) predicted Ibuprofen concentrations inside the feed frame and tablets' UV assay results vs time

The sample-to-sample concentration variation seen in case of NIR CI (area scan) is due to larger surface sampling by NIR CI (area scan) making it sensitive to surface distribution of the Ibuprofen as well as low signal-to-noise ratio over wavelength bandwidths allowed by the spectral filter.

5.5 Conclusion

Collectively, this work indicates that NIR CI (area scan) can be useful to trace gross changes in powder concentrations inside the feed frame however for quantitative concentration predictions for the purpose of strict quality control; there is a need for increasing the signal-to-noise ratio in NIR CI measurements. The poor signal quality in NIR CI (area scan) is due to variables such as wide wavelength range of spectral filter causing reduced specificity for active of interest, low intensity NIR emissions in the interested wavelength range causing lower NIR penetration, and low pixel resolution due to smaller sensor size representing larger sample area. Use of spectrograph (line scan) can help alleviate some of these limitations in NIR CI measurements.

CHAPTER 6 Simultaneous multiple components concentration monitoring inside the tablet press using NIRS and NIR CI (line scan)

Title in French:

Suivi simultané de la concentration de plusieurs composants par NIRS et NIR CI dans une presse à comprimés.

Summary

Content:

Chapter 5 demonstrated successful concentration predictions inside the feed frame using NIR CI (area scan image format using a wavelength bandwidth filter) but it also reported lower signal-to-noise ratio in the NIR CI (area scan) as compared to NIRS. NIR CI (line scan) using spectrograph can give spectral output similar to NIRS while giving spatial information as well. Thus, the present work evaluates NIR CI (line scan) to monitor 2 active ingredients in multicomponent pharmaceutical powder compositions. Calibration models prepared in off-line set up are evaluated for concentration prediction for in-line monitoring.

Results:

NIR CI (line scan) predicted the concentration of Ascorbic acid and Ibuprofen in close agreement with NIRS irrespective of the presence of multiple ingredients in the powder blend. Selection of wavelength ranges and spectral pre-treatments for respective actives are found as important parameters for performance of quantitative PLS models. Calibration model transfer from off-line testing to in-line monitoring was possible with removal of baseline variations in the spectral data. NIR CI (line scan) based concentration predictions in similar spatial location matched closely with NIRS. This shows that NIR CI (line scan) can be used to verify radial segregation by concentration prediction over the different spatial sections.

Contributions to the thesis:

This work presented the further advancement of NIR CI-based feed frame concentration monitoring in a much complex blend and simultaneously testing 2 active ingredients. NIR CI (line scan) not only gives similar spectral data as NIRS but also offers the opportunity to test radial segregation owing to larger spatial dimension covered by NIR CI with higher signal-to-noise ratio than NIR CI (area scan) with single waveband filters. Along with off-line model performance, transfer to in-line monitoring is also demonstrated. This chapter showed NIR CI (line scan) as a robust alternative for feed frame monitoring.

Abstract

Concentration monitoring inside a tablet press during manufacturing is important not only to assess the quality of the powder blend is compressed but it can also help to intervene and control the process by notifying adverse quality phenomena such as segregation. Near-infrared spectroscopy (NIRS)-based process analytical technology (PAT) has been successful for concentration monitoring in the press feed frame. However, it only tests small areas (e.g. 15×4 mm) of the powder sample. On the contrary, near-infrared chemical imaging (NIR CI) can potentially improve process monitoring owing to its comparatively larger sample area (e.g. 40×3 mm), thereby helping to detect local concentration changes as well as the presence of segregation. The present work reports simultaneous concentration monitoring of Ibuprofen and Ascorbic acid in a multi-component composition using both NIRS and NIR CI. Predictive models were built using Partial Least Square (PLS) analysis. The transfer of these models from lab to production has been evaluated to simultaneously predict the concentration variation of multiple ingredients inside the feed frame.

NIR CI (line scan) PLS models successfully monitor the Ibuprofen and Ascorbic acid concentrations despite the presence of multiple excipient ingredients influencing their individual spectra. To create successful PLS calibration models and subsequent concentration predictions, selection of NIR spectral wavelength ranges and pre-treatments are found as a critical factor. Transfer of calibration models from off-line tests to in-line monitoring is also feasible owing removal of baseline variations by the suitable spectral pre-treatments. NIR CI (line scan) predicted concentrations in a spatially similar powder area as tested by NIRS matched closely with NIRS-based concentration predictions. This finding suggests that NIR CI (line scan) can be potentially useful to probe the radial segregation inside the feed frame by the way of spatial concentration testing.

Keywords: NIRS; NIR CI (line scan); PAT; tablet; feed frame; segregation; model transfer

Résumé français:

Le suivi de la concentration dans une presse à comprimés durant la fabrication est important non seulement pour évaluer la qualité du mélange de poudre comprimé, mais aussi pour corriger et maîtriser le procédé en identifiant les attributs qualité défavorables tels que le démélange. La technologie d'analyse de procédé (PAT) basée sur la spectroscopie proche infrarouge (NIRS) est efficace pour le contrôle de la concentration dans la trémie d'alimentation de la presse. Cependant, elle ne teste que de petites zones d'échantillon de poudre (e.g. 15 x 4 mm). A l'inverse, l'imagerie chimique proche infrarouge (NIR CI) peut potentiellement améliorer le contrôle du procédé en raison de sa surface d'échantillon comparativement plus grande (e.g. 40 x 3 mm), aidant ainsi à détecter des changements de concentration locaux ainsi qu'un phénomène de démélange. Le travail actuel rapporte le contrôle simultané de la concentration de l'ibuprofène et de l'acide ascorbique dans une composition multi-composants en utilisant à la fois NIRS et NIR CI. Les modèles prédictifs sont construits en utilisant l'analyse des Moindres Carrés Partiels (PLS). Le transfert de ces modèles, du laboratoire à la production, sont évalués afin de prédire simultanément la variation de concentration de plusieurs ingrédients à l'intérieur de la trémie d'alimentation.

Les modèles NIR CI PLS contrôlent efficacement les concentrations d'ibuprofène et d'acide ascorbique malgré la présence de multiples excipients influençant leurs spectres individuels. Pour créer des bons modèles d'étalonnage PLS et des prédictions de concentration subséquentes, la sélection des plages de longueurs d'onde spectrales NIR et les prétraitements sont considérés comme des facteurs critiques. Le transfert de modèles d'étalonnage des essais hors ligne à la surveillance en ligne est également réalisable en raison de l'élimination des variations de la ligne de base par les prétraitements spectraux appropriés. Les concentrations prédites par la NIR CI dans une zone de poudre spatialement similaire, telle que testée par NIRS, correspondaient étroitement aux prévisions de concentration basées sur NIRS. Cette découverte suggère que la NIR CI peut être potentiellement utile pour sonder la ségrégation radiale à l'intérieur de la trémie d'alimentation par le biais de tests de concentration spatiale.

Mots-clés: NIRS; NIR CI (balayage de ligne); PAT; comprimé; plateau d'alimentation; ségrégation; transfert de modèles

6.1 Introduction

Pharmaceutical manufacturing is transitioning from a quality by testing approach to one of quality by design with multiple changes in drug regulatory scenario as a result of ICH Q8 (R2) [3], RTRT guidance [105], ICH Q9 [6], ICH Q10 [7], PAT guidance [2] and ICH Q11 [125]. Real time release (RTR) of pharmaceuticals has become a reality in recent years due to regulatory advocacy for process understanding, monitoring, control and use of technological advances by pharmaceutical manufacturers for this purpose. The implementation of real time release testing (RTRt) is an ideal state of pharmaceutical manufacturing which benefits both manufacturers as well as patients. Higher quality assurance is achieved via monitoring all of the critical processes and material parameters and ensuring they are within the desired limits throughout all the manufacturing process as opposed to traditional approach of testing certain fraction of final products batch to ensure the overall quality. RTRt also results in higher process control due to a better process understanding, improved efficiency and inventory control. However, for a successful RTRt implementation, a diligent identification of all critical manufacturing operations, critical product attributes and corresponding PAT applications for their monitoring must first be asserted.

6.1.1 RTRt in tablet manufacturing

In case of tablet manufacturing, a combination of in-process tablet weight, blend content uniformity measurement, drug substance purity and particle size could serve as a control strategy for drug content of a tablet if the relationship has been demonstrated. Monitoring of core tablet weight, blend uniformity, drug substance purity and particle size in this case are the RTR tests [105]. Tablet manufacturing involves different unit operations (mixing, milling, granulation, drying, compression, etc.) [126], which are critical for in-process and final product quality depending on the physicochemical properties of the tablet blend, manufacturing process i.e. based on wet or dry granulation. Among the different operations, tablet compression is one of the critical final operations irrespective of adopted manufacturing process i.e. dry granulation or wet granulation. During the tablet compression stage, blend concentration and its uniformity can only be tested at the hopper or in the feed frame. Monitoring blend concentration at the feed frame provides a better indication of final product properties considering the possibility of adverse quality phenomenon i.e. segregation while the

material is in continuous high speed movement. Segregation can occur due to influence of multiple factors e.g. differences in material particle size. [19], density differences [127], shape [128], moisture [129], speed of powder movement [53].

6.1.2 NIRS in feed frame monitoring

NIRS PAT applications for concentration monitoring at the feed frame are rising in last few years due to its speed, flexibility, and the in-line manner implementation. NIR has been successfully implemented for concentration monitoring inside the feed frame in the range of 2-30 % w/w [52][16]. Concentration monitoring can be performed by tracking changes in spectral intensity of single wavelength [61] or a range of wavelengths [15] by means of chemometric methods such as PCA and PLS. Most of the earlier works on monitoring feed frames using NIRS reports the monitoring of only single ingredient at a time. However, in practice, there is often more than one ingredient of interest in the tablet composition. NIRS spectra of most pharmaceutical ingredients are complex in nature [130] and show overlapping regions of NIR absorbance due to common functional groups. Thus, making accurate quantitative models for concentration monitoring, especially in the presence of multiple NIR active ingredients, could be challenging and needs to be studied.

Preparation of NIRS-based in-line quantitative concentration models has been reported in earlier work; however transferring quantitative models from one batch to another or from lab to production has not been successful. Different methods of NIRS calibration model transfer have been reported [131] [132] in the literature but most of them require extensive time and resource investment. In case of feed frame monitoring, additional factors such as continuous motion of the sample, density changes and baseline variations pose challenges in calibration transfer since they can contribute to variation in NIR spectral data [15]. In this study, the use of spectral pre-treatments to remove unwanted spectral variations while transferring the calibration method from batch to batch or lab to production needs was evaluated.

6.1.3 NIR CI in feed frame monitoring

Along with NIRS applications, NIR CI (area scan) using a wavelength band filter has also been reported for feed frame concentration monitoring owing to both spectral and spatial information it provides which could detect adverse quality phenomenon like segregation

[133][134]. In case of multi-component mixtures, NIR imaging of the sample over multiple wavelength bands or considerable range of NIR spectrum is required. This could be achieved via multiple filters, but adjusting the NIR imaging parameters (especially to accommodate variations of NIR source intensity and filter transmitted light intensity) at different filters as well as material movement inside the feed frame poses challenges in successful data acquisition at the same time it leads to temporal delays between the wavelengths. In this regards, the amount of spectral information in a single image can be dramatically increased by combining it with a spectrograph rather than using multiple filters. Though we lose on spatial component for one spatial dimension (e.g. length) but we maintain information over the other spatial dimension (i.e. width) of the sample. For moving samples like inside feed frame, variation along width (signifying spatial concentration changes) is important than length since radial segregation is more prone under centrifugal force of the rotating paddles. A spectrograph offers spectral information over a range of discrete wavelengths instead of certain wavelength band as offered by single filter. As a result, NIR CI (line scan) gives spectral data similar to NIRS but covers a larger sample area.

6.1.4 NIRS and NIRCI for concentration monitoring inside feed frame

The present work aims at evaluating simultaneous concentration monitoring of a multicomponent powder blend comprising Ibuprofen and Ascorbic acid inside a feed frame as well as to evaluate the possibility of the transfer of calibration model from lab to production and from one batch to another. The impact of selecting different wavelength ranges and different spectral pre-treatments on the qualitative (principal component analysis - PCA) and quantitative (partial least square - PLS regression) models has also been studied. More specifically, the effect of spectral pre-treatments on the NIRS baseline was evaluated to study the feasibility of calibration model transfer. Since spatial concentration variations inside the feed frame are the main indicator of segregation of the active ingredient, a model was built to predict the concentrations in different sections of a feed frame using NIR CI (line scan). Quantitative concentration predictions by NIRS-based PLS models inside the feed frame are compared with NIR CI (line scan)-based predictions. Finally, concentration change kinetics for Ibuprofen and Ascorbic acid are compared by both NIRS and NIR CI (line scan) methods to compare relative performance of NIR CI (line scan) and NIRS to detect concentration change inside the feed frame.

6.2 Materials and methods

Experimental work was carried out in 2 stages, off-line (away from tablet press, just using a table top feed frame set-up) and in-line (using feed frame on tablet press).

6.2.1 Materials

Materials used in this study consisted of Ibuprofen coated pellets (Adare pharmaceuticals, Vandalia, Ohio, USA), Ascorbic acid granules (DSM, Jiangsu, China), mannitol (Roquette, Keokuk, IA, USA), microcrystalline cellulose (Avicel PH 101^r, FMC biopolymer, Philadelphia, PA, USA), sodium starch glycolate (Roquette, Lestrem, France), colloidal silicon dioxide (Aerosil^r 200 pharma, Evonik, Parsippany, NJ, USA) and magnesium stearate (Mallinckrodt, St. Louis, MO, USA). Particle size of Ibuprofen pellets (d80), mannitol (d85), microcrystalline cellulose (d90) and Ascorbic acid granules (d70) was 420-177 μm , 500-104 μm , 77-156 μm and 150-850 μm respectively. In Ibuprofen pellets, 2% of total particles were larger than 420 μm , while in Ascorbic acid granules, 20 % of the particles size was above 850 μm .

6.2.1.1 Formulation composition

Tablet blend composition in the present work consisted of 2 active ingredients at different concentrations namely Ibuprofen (available in pellet form coated with gelatin and cellulose acetate phthalate) and Ascorbic acid (available in granule form). Seven (7) blends with varying content of Ibuprofen and Ascorbic acid were prepared ensuring nonlinear change with respect to one another. All excipients other than magnesium stearate compensated the change in weight of Ibuprofen pellets and Ascorbic acid granules as shown in table 1. Bulk excipient (mannitol and microcrystalline cellulose) concentrations were varied in proportion to Ascorbic acid and Ibuprofen, while minor excipients (colloidal silicon dioxide, sodium starch glycolate and magnesium stearate) were maintained at the same concentration for all blends. Batch size was set to 12.0 kg, due to equipment capacities, desired tablet compression rate and the time necessary for concentration stabilization inside the feed frame. During the blend preparations all ingredients except magnesium stearate were added in the V blender (Patterson Kelly, USA) and rotated for 15 min at 26 rpm. Following this, magnesium stearate was added and mixing continued for 2 more minutes. At the end of mixing, all blends were transferred in a double lined polythene bag and used for tablet compression.

Table 6.1: Formulation composition with different levels of Ibuprofen and Ascorbic acid (all concentration values are in % w/w)

Blend composition	A	B	C	D	E	F	G	H	I
Ibuprofen pellets	8.0	8.0	8.0	12.0	5.0	12.0	10.0	6.5	10.0
Ascorbic acid granules	0.0	5.0	15.0	0.0	0.0	10.0	7.5	2.5	5.0
Mannitol	75.4	71.0	62.3	71.9	78.0	63.1	67.1	74.5	69.3
Microcrystalline cellulose	10.8	10.2	8.9	10.3	11.2	9.1	9.6	10.7	9.9
Colloidal silicon dioxide	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Sodium starch glycolate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

As shown in table 6.1. Ibuprofen pellet content was varied in the range of 0-12 % which in reality corresponded to 0-10.2 % w/w Ibuprofen, considering pellet assay value (85 % w/w Ibuprofen). For Ascorbic acid, concentration varied from 0-15 % which corresponded to 0-13.5%, considering Ascorbic acid granules assay (90% w/w of Ascorbic acid). However, blends are referred herein according to total % w/w Ibuprofen pellet and Ascorbic acid granules content. Random blend order with respect to both active ingredient concentrations was adopted during tablet compression to minimize concentration change correlation of the two active ingredients. Blend compositions A-J described in Table 1 also presents the order in which blends were processed. Smallest step change in Ibuprofen and ascorbic acid concentrations occurred between blend F-G and H-I/F-G while highest step change occurred between D-E/E-F and C-D respectively. Such a sequence allowed to study the NIRS response to varying concentrations inside the feed frame as well as to clearly outline the 5 steady states in order to help quantify step-change dynamics. During the off-line testing, blends A-F were used in the preparation of PLS calibration models while blends G-I were used in validation of these models. Blends G-I were prepared by mixing 300 gm of blend from each of C and D, B and E, A and F respectively.

6.2.2 Equipment and Methods

6.2.2.1 Feed frame monitoring (In-line)

This study used a Manesty Novapress 37-station rotary tablet press with a feed frame. Details of feed frame design are reported in earlier publication [123].

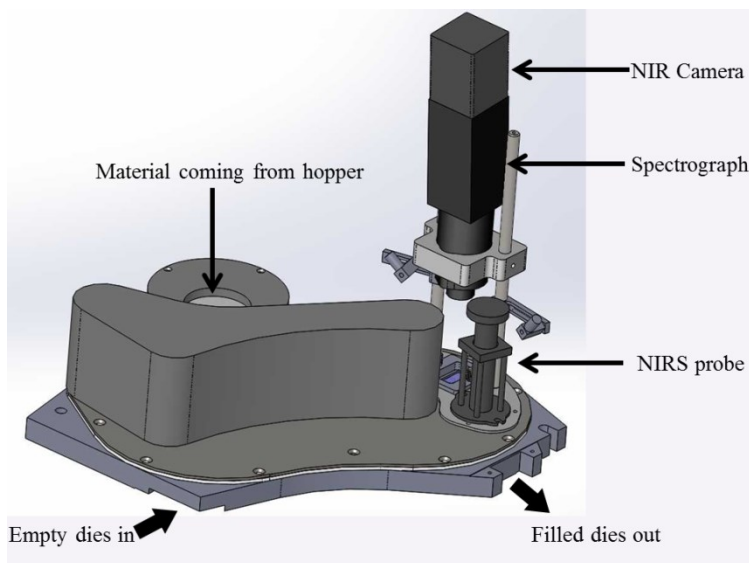


Figure 6.1 : NIRS and NIR CI (line scan) location on the feed frame

The NIR probe was placed above the second wheel just before the point where powder exits the feed frame and enters the die cavities for compression. The NIR Camera and its attached spectrograph were positioned just before and as close as possible to the NIR probe. The NIR probe tip was positioned using a micrometer screw ensuring its contact with the powder while preventing contact with the paddle wheel. In order to study the impact of the position of the NIR probe with respect to the paddle distance, off-line testing was performed with a probe to paddle distance of 8 mm while in-line testing was performed with a probe to paddle distance of 2 mm. For the NIR CI (line scan), the feed frame to spectrograph distance was adjusted to maximize the desired feed frame area in the captured images. Data acquisition was triggered by a sensor attached to the feed frame shaft. Two NIR spectra and NIR CI (line scan) were recorded at each rotation of the paddle wheel. NIRS probe and NIR CI (line scan) parameters with respective acquisition settings are listed in table 6.2.

Table 6.2: NIR spectral acquisition parameters

PAT tool	Spectral range (nm)	Resolution (nm)	Integration time per spectra (ms)	Number of spectra averaged	Total integration time (ms)
Viavi NIR probe	915-1701	6	5	50	250
NIR Camera + Spectrograph	900-1700	3	3	1	3

600 gm of the powder sample was taken from each respective blend and used for off-line test while remaining blend was used in the in-line test. During the off-line test, each blend was added sequentially in a closed feed frame rotated at 20 rpm and NIRS as well as NIR CI (line scan) signals were collected at a rate of two per revolution of paddle wheel. After collecting NIR spectral data for 10 min, care was taken to completely remove the respective blend before adding the next one inside the feed frame.

During the in-line tests, tablet compression was performed at a rate of 18360 tablets per hour (17 stations at 18 rpm). Feed frame paddle wheel rpm was adjusted at 18 rpm to obtain consistent tablet weight. NIRS spectra and NIR CI (line scan) were recorded at a rate of one per revolution of feed frame paddle wheel. Throughout this publication, this in-line test is referred to as first in-line tests.

Data from earlier in-line tests were used for the calibration model transfer from one batch to another. In this case, tablets were compressed at a rate of 23,460 per hour. Feed frame paddle wheel rpm was adjusted at 13 rpm to obtain consistent tablet weight. NIR probe was located 8 mm away from the paddle wheel. 1 NIR signal was collected at each revolution of the paddle wheel. Other details of the composition and set up can be found in earlier publication. Throughout this publication, this in-line test is referred to as second in-line test.

6.2.2.2 NIRS data acquisition and pre-treatment

Before NIRS data acquisition, the intensity of the NIR probes (Viavi) was calibrated between 0 and 100% reflectance. For the 0% set-up, a NIR spectrum was acquired in absence of infrared light while for the 100% set-up, NIR spectrum was recorded while the intensity of

the NIR beam was set at 100% reflectance. Every raw spectrum acquired during the trials was corrected between 0% and 100% reflectance standards (equation 6.1):

$$C = \frac{R-D}{B-D} \quad (6.1)$$

where C is the corrected spectra, R is the raw spectra, D is the 0% reflectance (dark) standard and B is the 100% reflectance (bright) standard.

Collected NIR spectra inside the feed frame contained Ibuprofen and Ascorbic acid concentration information; but were tainted by other variables detrimental to the building of PLS models, such as variations in material movement at different paddle speeds, powder to probe distance and difference in particle sizes. In order to remove the unwanted spectral features, spectral pre-treatments such as standard normal variate (SNV- for scatter correction), Savitzky-Golay first derivative (SG-D1), Savitzky-Golay second derivative (SG-D2- for resolving peak overlap, eliminating linear baseline drift between samples), multiple scatter correction (MSC- for minimizing baseline offsets and multiplicative effect), centering and scaling to unit variance (CS) as well as subtracting a polynomial fit to reduce any baseline variation were evaluated for their suitability in qualitative and quantitative analysis (calibration as well as prediction).

6.2.2.3 NIR CI (line scan) data acquisition and pre-treatment

An observation window (Figure 6.2a) was made across the width of the feed frame which allowed having NIR CI (line scan) covering the entire powder region (40×3 mm) inside the feed frame. NIR CI (line scan) output was obtained in the form of 256×320 matrix (Figure 6.2b) in which X-axis represented spatial dimension while Y-axis represented spectral information, with a resolution of 143 micron per pixel. The intensity of all of the NIR CIs was corrected with a white and dark standard which were recorded just before the start of sample data acquisition each time to standardize pixel intensities. The intensity of each NIR CIs was averaged over the spatial axis to get an output spectrum (Figure 6.3c). Thus powder area of 40×3 mm was represented by a single spectra as against of NIRS which represent powder area of 15×4 mm. Spectral axis of the NIR CI (line scan) was calibrated using the spectrum obtained from images of known spectral standards.

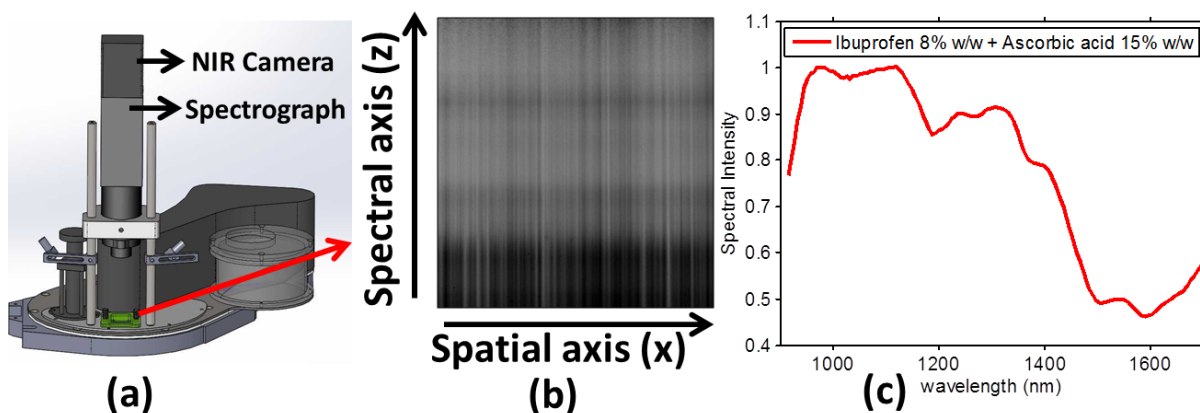


Figure 6.2: a) Location of the observation window on the feed frame, b) NIR CI (line scan) output image and c) NIR spectra obtained by averaging all of the image pixels.

NIR CI (line scan) data was affected with certain unwanted variable such as variation in NIR light intensity, powder density changes under circulation inside feed frame which were likely to create a bias in the predictability of the calibration models from off-line to in-line samples, thus various spectral pre-treatments as mentioned in section 6.2.2.2 were used to remove the spectral artifacts.

6.2.2.4 NIRS Wavelength selection

Excipients or other ingredients with strong NIR absorbance (e.g. water/moisture) at the same range or in the vicinity of the interested NIR range can either mask or change the shape of active ingredient NIR absorbance spectra. Earlier studies using a single filter NIR CI (global) for Ascorbic acid (chapter 3) and NIRS of Ibuprofen (chapter 5) gave an indication for wavelength selection in the present work. However in these cases, powder blends had only one ingredient of interest, with little possibility of spectral overlap or interactions. For the purpose of NIR wavelength selection, characteristic spectral bands of Ibuprofen and Ascorbic acid were determined via the Savitzky-Golay second derivative spectral plot (Figure 6.3).

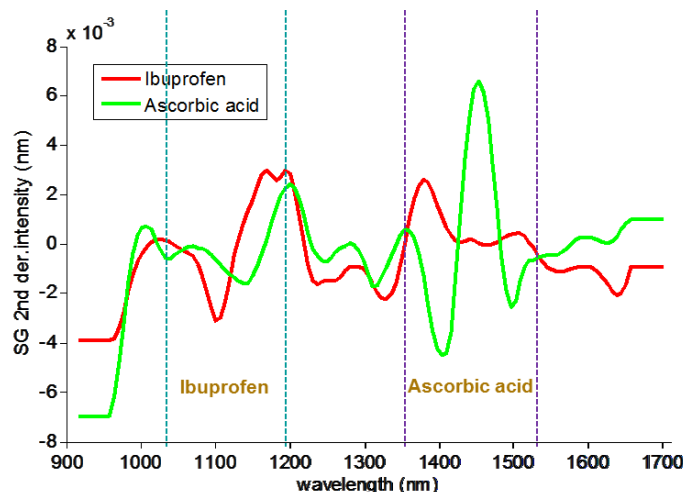


Figure 6.3: Savitzky-Golay second derivative spectra of Ibuprofen and Ascorbic acid

Both Ascorbic acid as well as Ibuprofen show characteristic peak shapes in NIR spectral region between 1000-1700 nm, but show higher or lower NIR absorbance in certain regions, e.g. 1020 to 1200 nm (Ibuprofen) and 1350 to 1550 nm (Ascorbic acid) making it possible to differentiate respective concentrations using these ranges. In the composite blends however, other ingredients dilute these spectral differences which can have an influence on the evaluation of the concentration of the active ingredient in the tablet blend.

Figure 6.4(a) shows key individual ingredients' NIR spectra while figure 6.4(b) shows NIRS spectra and 6.4(c) shows NIR CI (line scan) spectra of all the blends used in the study. Comparison of individual and composite blend NIR spectra reveals that Mannitol dominates the NIR spectra. This is to be expected as it is present in the highest concentration of all ingredients of the blends (≈ 70 wt %). PCA was used to select the spectral wavelengths and pre-treatments to be included in the quantitative analysis, focusing on the spectral range of each active's peculiar peaks as well as the spectral the range in their vicinity. A suitable NIR range and pre-treatment was determined based on the criteria that changes in principal components score values exhibit the changes in concentration of the respective active in the blends.

Wavelength ranges 1020-1305, 1020-1212 and 1100-1250 nm were evaluated for Ibuprofen while 1373-1701, 1354-1552 and 1472-1602 nm were evaluated for Ibuprofen. Wavelength ranges and respective pre-treatments which showed desired concentration trends in PCA scores were selected further for quantitative analysis using PLS. Calibration model parameters such as the root mean square error of calibration (RMSEC), root mean square error

of cross validation (RMSECV) and root mean square error of prediction (RMSEP) for predicted concentrations were used to evaluate the suitability of the wavelengths selection for the quantitative models.

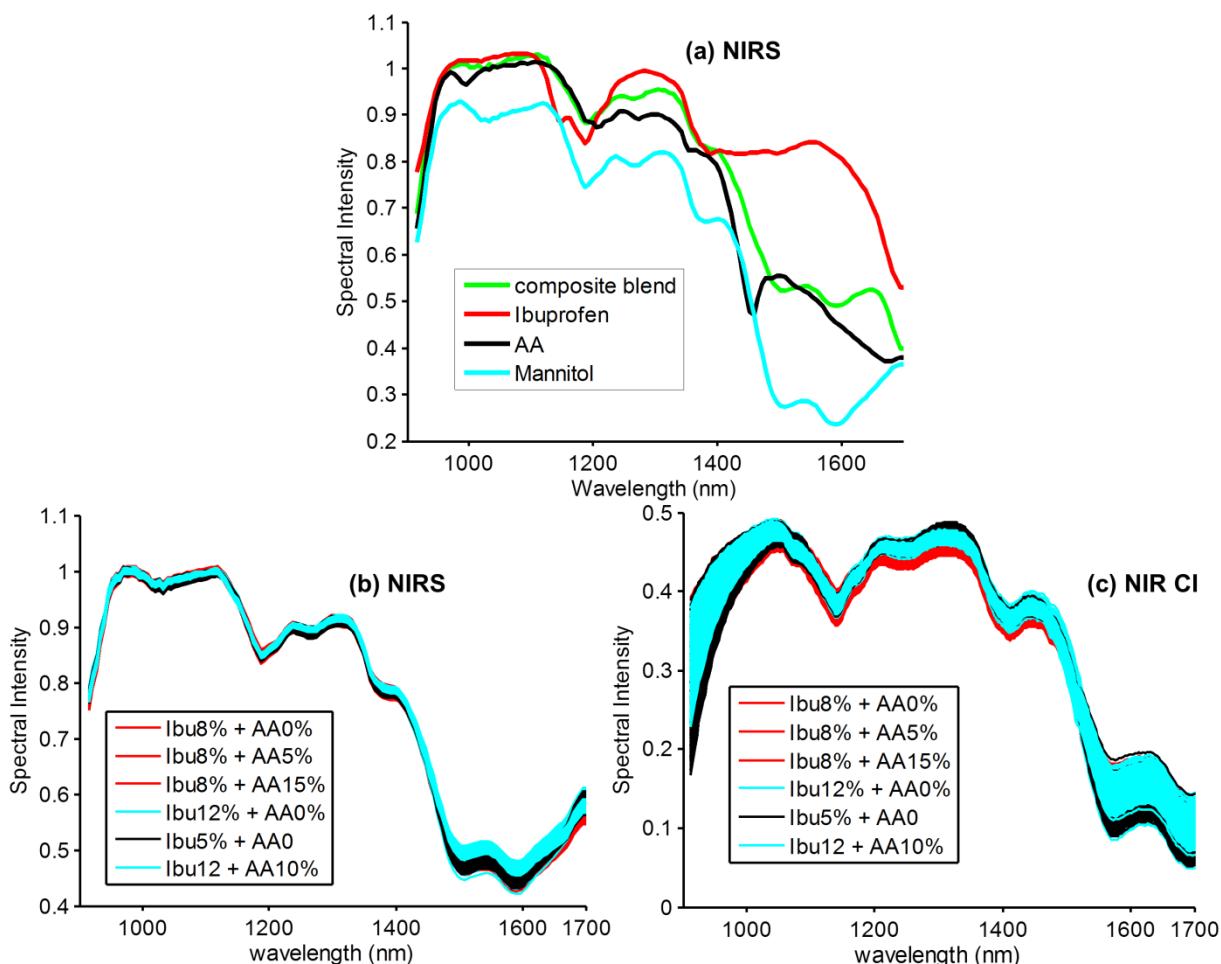


Figure 6.4: a) NIRS spectra of key ingredients of the tablet composition and b) NIRS spectra c) NIR CI (line scan) spectra of all blends in off-line trial

6.2.2.5 PLS calibration and validation models

For off-line test, PLS calibration models (based on NIRS as well as NIR CI (line scan)) for Ascorbic acid and Ibuprofen were prepared using blend samples A-G and validated using blend samples H-J prepared only for the purpose of validation in off-line test. These validated calibration models were used for predicting the concentration of Ibuprofen and Ascorbic acid in the respective data (NIRS and NIR CI (line scan)) of the in-line test. The intention here was

to show the feasibility of PLS calibration transfer from lab to production (i.e. off-line to in-line).

6.2.2.6 Comparison of NIRS and NIR CI (line scan) predictions inside feed frame

As mentioned earlier, NIR CI (line scan) gives an image covering the entire powder surface in horizontal direction (40 mm) of the feed frame, while covers only 3 mm in powder flow direction. While NIR probe observation window size is 15×4 mm. NIR probe is placed in the middle of feed frame horizontal cross section. Thus, the powder area tested by NIRS is comparable with middle section of NIR CI (line scan) when divided in 3 equal parts. Thus, PLS model predicted concentrations of ascorbic acid and ibuprofen at the middle sections NIR CI (line scan) are compared to concentrations predicted by NIRS as well as the expected concentrations using the root mean square error (RMSE).

6.2.2.7 Sample volume inside feed frame

The NIR sample volume is an important parameter to study the level of scrutiny in in-line process monitoring since the effective sample volume in blend uniformity analysis should be comparable to a unit dose [22]. The sample volume was estimated using the NIRS sample area/spot size of NIRS probe, integration time, material bulk density and NIR penetration using equation 6.2.

$$\text{Sample Volume} = A \times B \times C \quad (6.2)$$

where A is the NIRS sample area, B is the NIR penetration depth, and C is the sample bulk density.

Inside the feed frame, the NIRS sample area and total integration time was 15 × 5 mm and 5 ms respectively. Each NIR spectra was averaged over 50 spectra, thus total integration time is 250 ms. The sample area was calculated considering the material movement within this time based on the feed frame rpm. The NIR penetration depth was considered as 1.5 mm, according to earlier studies [123]. In the case of NIR CI (line scan), the sample area covered by each image was 40 × 3 mm, while NIR penetration depth was considered as 0.75 mm based on earlier studies [123].

Sample volume tested by NIRS was found to be 67.5 mg while NIR CI tested 47.25 mg. Sample volumes in case of NIR CI (line scan) is slightly lower than NIRS, mostly due to higher NIR penetration depth in NIRS compared to NIR CI. However, larger length of sample

helps in efficient concentration monitoring owing to complete powder sample coverage in the horizontal direction.

6.3 Results and discussion

6.3.1 Off-line NIRS PLS calibration models

NIRS PLS model parameters using 1020-1305 nm wavelength range, SNV, SG-D1, centering and scaling in spectral pre-treatments gave the best PLS model for Ibuprofen, i.e. lowest RMSEC, RMSECV and RMSEP values as 0.33, 0.33 and 0.41 % w/w Ibuprofen respectively. An adjusted R^2 (R^2_{adj}) value of 0.98 (with 3 latent variables) also showed a good model fit to the calibration data.

In the case of Ascorbic acid, suitable wavelength range was found to be 1373-1701nm with SNV, SG-D1, centering and scaling in spectral pre-treatments. PLS model parameters like RMSEC, RMSECV and RMSEP showed values of 0.54, 0.54 and 0.80 % w/w Ascorbic acid respectively while R^2_{adj} was 0.98 (with 3 latent variables). These PLS model parameters indicated good model fit and model performance for Ascorbic acid calibration and validation samples respectively.

PLS models for both the actives show similar level of fit to calibration data based on R^2_{adj} using 3 latent variables. PLS model parameters like RMSEC, RMSECV and RMSEP are slightly higher for Ascorbic acid than Ibuprofen indicating slightly higher sample to sample variation in case of Ascorbic acid. These variations could be attributed to wide particle size distribution of ascorbic acid (more details on PSD are given in section 6.2.1). However, considering the concentration levels of the Ascorbic acid in the current formulations these values are well acceptable.

Figure 6.5a and 6.5b show that the PLS model predicted concentrations are closely distributed around the expected concentration for both the active ingredients. The optimal wavelength range showing good model fit and concentration prediction for Ibuprofen (i.e. 1020-1305 nm), is comparatively broader than the earlier wavelength range (1100-1250 nm-chapter 4) useful to precisely quantify the different Ibuprofen concentrations where it was single active of interest. Thus, it appears that in the presence of multiple ingredients, a broader spectral range selection outperforms the use of a few characteristic peaks of individual active

when building a quantitative model. This is attributed to masking influence of other components on the NIR peak of active.

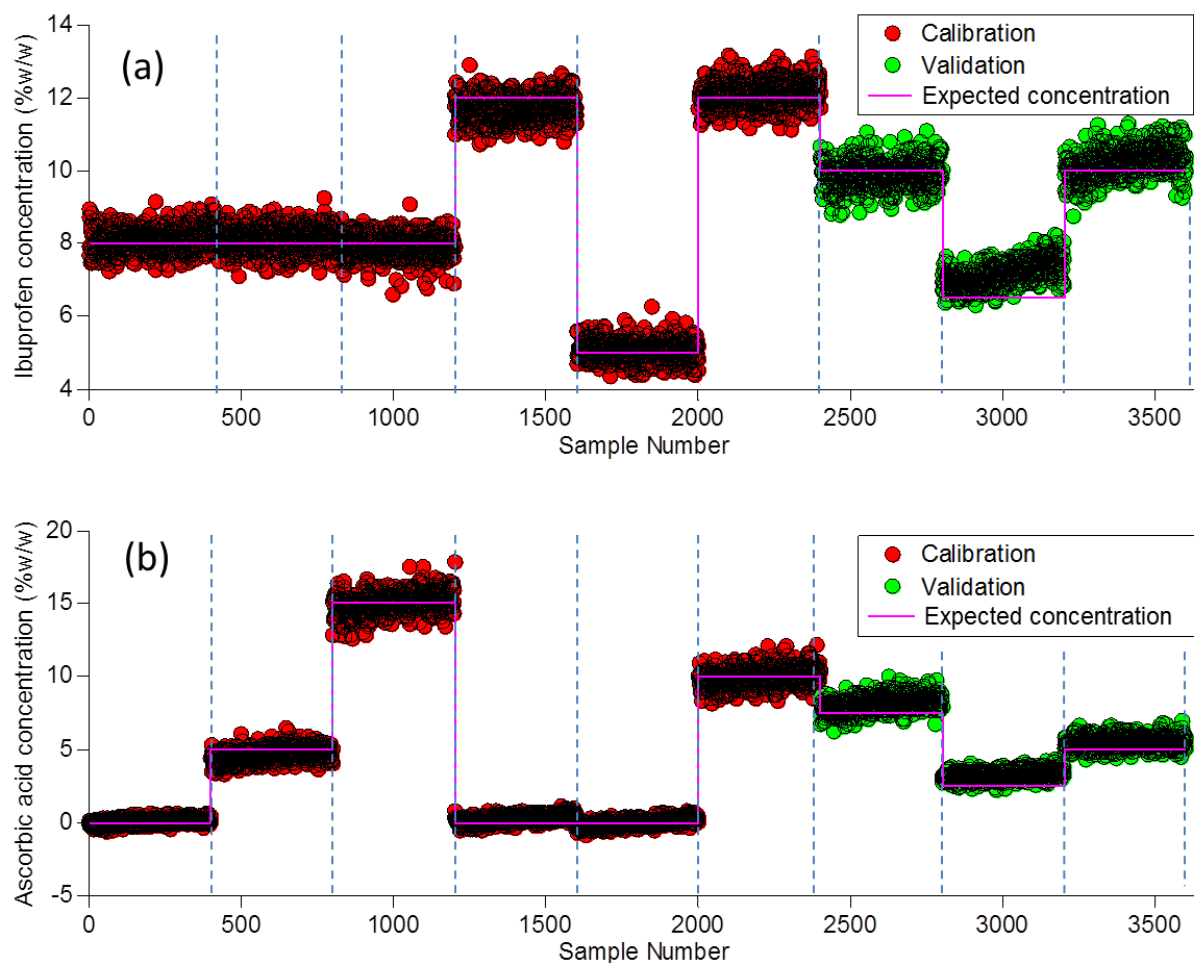


Figure 6.5: NIRS PLS predicted a) Ibuprofen and b) Ascorbic acid concentrations in calibration and validation samples

6.3.2 Off-line NIR CI (line scan) PLS calibration models

NIR CI (line scan) PLS model for Ibuprofen using 1018-1213 nm wavelength range and SG-D1, SNV followed by scaling to unit variance and centering in pre-treatment exhibited good PLS model parameters i.e. RMSEC, RMSECV and RMSEP of 0.59, 0.59 and 1.05 respectively. R^2_{adj} value using 3 latent variables was 0.94 which is slightly lower than the NIRS PLS model. The RMSEC, RMSECV and RMSEP values are also slightly higher than the NIRS PLS model. This indicates that NIR CI (line scan) PLS model is slightly less precise in comparison to NIRS.

In case of Ascorbic acid, wavelength range between 1372-1701 nm with SNV, SG-D2 followed by mean center (MC) gave good model parameters i.e. RMSEC, RMSECV and RMSEP as 1.01, 1.02 and 1.05 respectively. R^2_{adj} using 3 latent variables, was 0.96 which is slightly lower than the NIRS PLS model.

For Ascorbic acid, the same wavelength range (1372-1701 nm) as in NIRS was found suitable for NIR CI (line scan) while in case of Ibuprofen, slightly lower wavelengths exhibited better PLS model parameters. Visual comparison of PLS calibration and validation concentration plots of NIR CI (line scan) (Figure 6.6a, 6.6b) with NIRS (Figure 6.5a, 6.5b) reveals that Ibuprofen concentrations show similar spread around the expected concentration while Ascorbic acid concentrations show comparatively higher spread around the expected concentration.

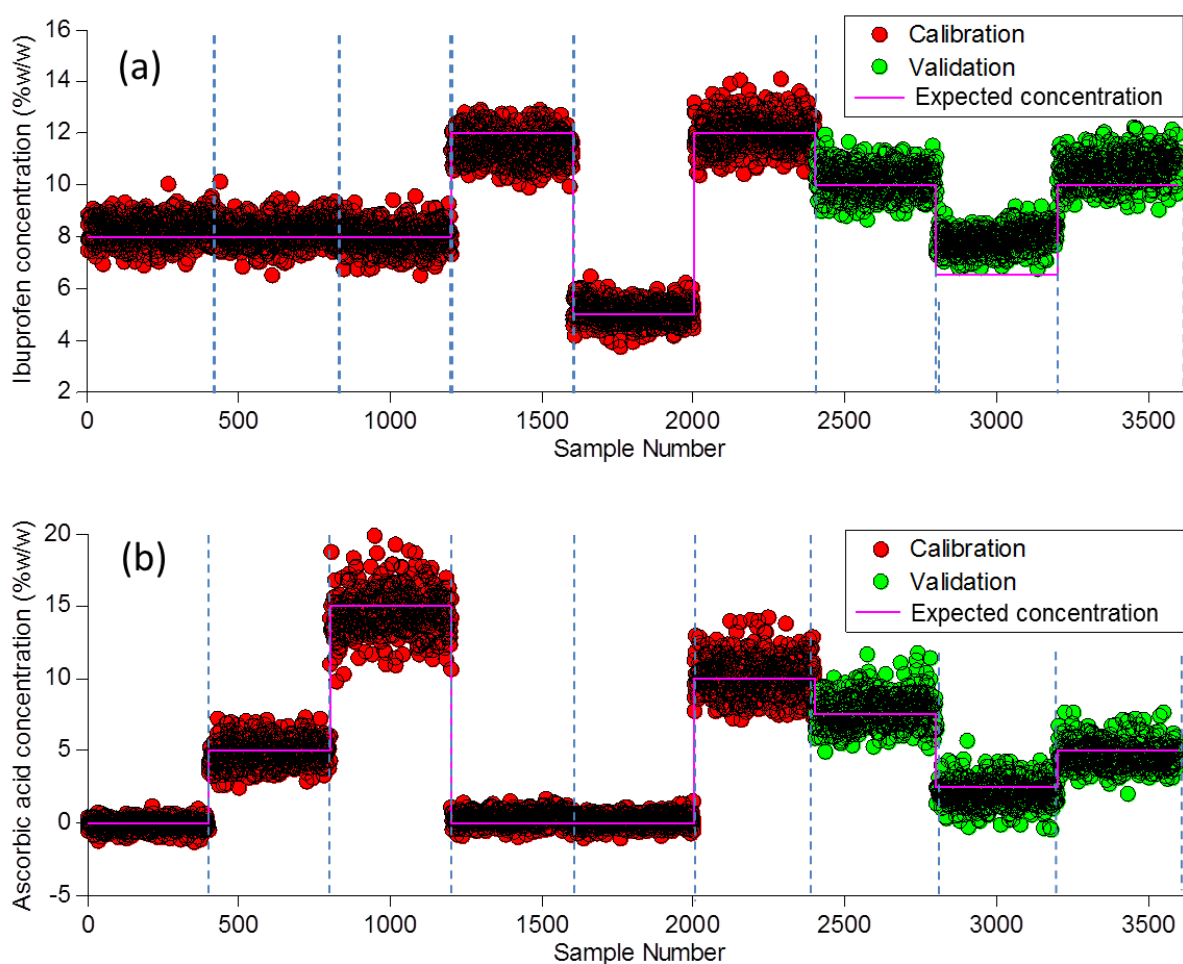


Figure 6.6: NIR CI (line scan) PLS predicted a) Ibuprofen and b) Ascorbic acid concentrations in calibration and validation samples

6.3.3 Comparison of NIRS and NIR CI (line scan) for concentration prediction

RMSE in NIRS PLS concentration predictions

RMSE values calculated between NIRS predicted and expected concentrations showed that NIRS PLS model for Ibuprofen has RMSE value of 0.25 while for Ascorbic acid RMSE value was 0.64 indicating that Ibuprofen concentrations were predicted close to expected concentration than the Ascorbic acid. The difference in RMSE values is attributed to wider particle size distribution of Ascorbic acid in the blend as compared to Ibuprofen which leads to slightly higher spectrum to spectrum variance. However these values are less than 1.0 % w/w which is deemed acceptable in the present case.

RMSE in NIR CI (line scan) PLS concentration predictions

RMSE values between expected concentrations and NIR CI (line scan) predicted Ibuprofen and Ascorbic acid concentrations were found as 0.78 and 1.03 respectively. These values are slightly higher than NIRS PLS models but acceptable owing to the concentration levels of respective actives in the present formulations. RMSE values between NIRS PLS predicted concentrations and NIR CI (line scan) predicted Ibuprofen and Ascorbic acid concentrations were found as 0.72 and 1.21 respectively. Comparatively the RMSE values shown by NIR CI (area scan) at similar concentration levels of Ibuprofen were in the range of 2-3 (section 4.2); this shows that signal-to-noise ratio is better in case of NIR CI (line scan) than NIR CI (area scan).

Variance comparison

Variation in the NIRS and NIR CI (line scan) predicted concentrations were assessed to compare signal-to-noise ratio in the collected spectral data assuming all the blends were uniform and only interference in model prediction is signal-to-noise ratio in collected data. As seen from figure 6.7 and 6.8, NIR CI (line scan) predicted concentrations show higher variance than NIRS predicted concentrations for both the actives. Variance in Ibuprofen concentration prediction at similar concentration levels using NIR CI (area scan) was more than 3 (Figure 5.4) while the variance with NIR CI (line scan) PLS models, it is less than 0.45 (% w/w)² of Ibuprofen. This indicates that NIR CI (line scan) gives more precise sample information than NIR CI (area scan).

NIR CI (line scan) PLS predicted Ascorbic acid concentrations show higher variance than Ibuprofen, indicating that sample-to-sample variance in case of Ascorbic acid is higher.

As mentioned earlier, it is attributed to image to image variation in the surface distribution of Ascorbic acid due to wide particle size distribution, when a particularly larger granule of Ascorbic acid is on the surface the predicted concentration is comparatively higher than the average blend concentration. Other factors that contribute to higher sample-to-sample variation are the sample surface area tested by NIR CI (line scan) is larger than NIRS and lower NIR penetration depth value in NIR CI; which is found as 0.75 mm (chapter 3) with NIR illumination source used in this work. Collectively these factors make NIR CI sensitive to surface distribution of active particles when particle size variation in the sample is higher. In the present samples Ascorbic acid has wider particle size distribution than Ibuprofen (section 6.2.1).

Variance in NIR CI (line scan) predicted Ibuprofen concentration was not drastically higher than NIRS since it has more uniform particle size as compared to Ascorbic acid. However, variance in NIR CI (line scan) predictions is still slightly higher than NIRS which points to comparatively smaller signal-to-noise ratio in NIR CI (line scan) than NIRS. Comparative study of variance values helps to signify importance of particle size, tested sample area and NIR penetration depth in the sample for NIR PLS model performance.

Irrespective of small differences as discussed above for NIRS and NIR CI (line scan) predicted concentrations, the off-line PLS calibration models proved that both these actives (Ascorbic acid and Ibuprofen) can be simultaneously quantified without interference from the other.

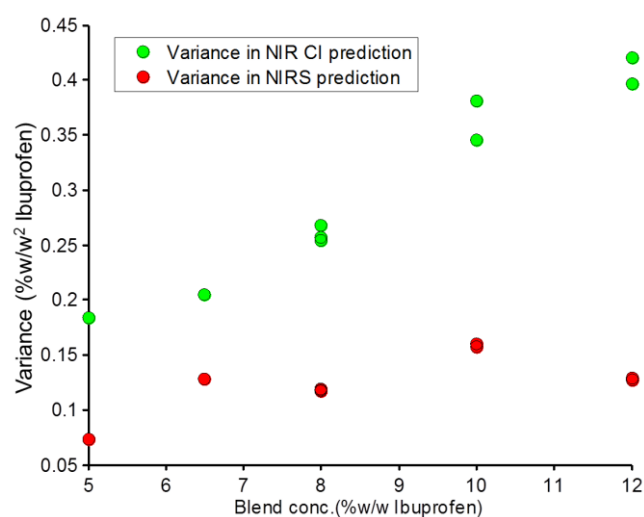


Figure 6.7: Variance in predicted Ibuprofen concentrations comparing NIR CI (line scan) and NIRS PLS models

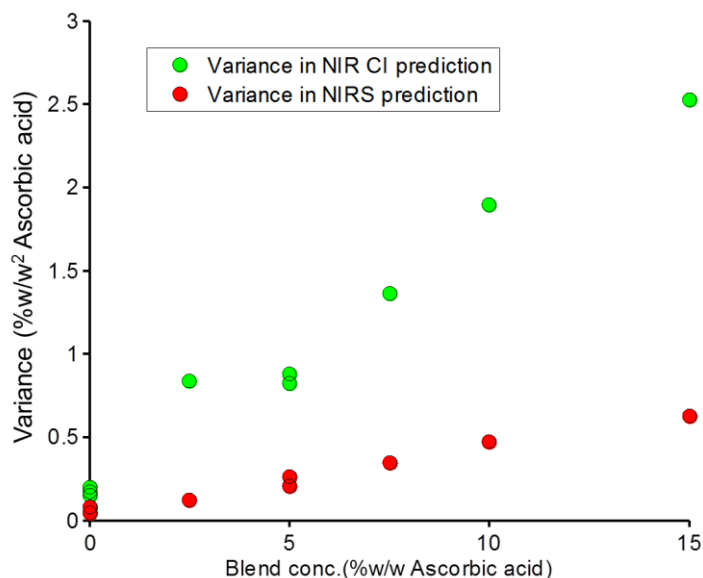


Figure 6.8: Variance in predicted Ascorbic acid concentrations comparing NIR CI (line scan) and NIRS PLS models

6.3.4 Calibration model transfer off-line (lab) to in-line (production)

Following the successful concentration predictions in the off-line testing, the best performing calibration models (both NIRS and NIR CI (line scan)) were used to predict Ibuprofen and Ascorbic acid in the in-line tests.

The blends used to make off-line calibration models were taken from the same bulk blends which were used in the in-line test, thus respective off-line PLS models were expected to predict exactly the same concentrations during the in-line test. However, it was found that the predicted in-line concentration was slightly off the expected concentrations. The trend in the concentration variations was predicted well but the absolute values of the concentrations were shifted either to lower or higher values. The shift in NIRS predicted concentrations were comparatively smaller than the concentrations predicted by NIR CI (line scan).

Off-line PLS models do not give the desired predictions as expected from blend concentrations, probably due to additional variations in the NIR spectral data as a result of different experimental conditions such as paddle wheel rpm, probe to paddle distance, etc. Careful examination of the NIRS and NIR CI (line scan) spectra showed differences in spectral baseline between off-line and in-line test samples. The baseline shift between the off-line and in-line NIRS tests is attributed to the differences in the paddle to powder distance as well as in feed frame paddle wheel rpm. For the off-line test, NIR probe was 8 mm away from

paddle wheel while for the in-line test it was 2 mm away from the paddle. The feed frame rpm for the off-line and the in-line test was 24 and 17 respectively.

Presence of baseline variation in the NIR CI (line scan) data indicates that in addition to the feed frame variables (e.g. paddle speed), other parameters such as NIR light intensity and sample illumination are also important variables in the successful transfer of NIR CI (line scan)-based PLS calibration model. In order to remove the baseline shifts, spectral pre-treatments were applied and assessed based on the difference between the expected and predicted concentrations. The removal of the baseline shift, or detrending, was performed through a subtraction of a linear or polynomial fit of the baseline from the Ibuprofen and Ascorbic acid NIR and NIR CI (line scan) spectra in addition to other spectral pre-treatments.

Off-line NIRS PLS model with 3 latent variables for Ibuprofen using 1020-1305 nm wavelength range, SG-D1, detrend (offset), SNV, centering and scaling in spectral pre-treatment showed R^2_{adj} value of 0.98 while RMSEC and RMSECV of 0.36 and 0.36 respectively. NIRS PLS model with 3 latent variables for Ascorbic acid using 1373-1701 nm wavelength range, SG-D1, detrend (6th order), SNV, centering and scaling in spectral pre-treatment showed R^2_{adj} value of 0.99 while RMSEC and RMSECV of 0.56 and 0.56 respectively. This indicates that there is no significant impact of additional baseline removal on the earlier off-line PLS models (section 6.3.2) except that the new models are now capable to predict in-line concentrations without any shift in values.

In case of NIR CI (line scan), PLS model with 3 latent variables for Ibuprofen using 1018-1213 nm wavelength range, SG-D2, SNV, detrend (6th order), centering and scaling in spectral pre-treatment showed R^2_{adj} value of 0.93 while RMSEC and RMSECV of 0.68 and 0.68 respectively. Off-line PLS model with 3 latent variables for Ascorbic acid using 1372-1701 nm wavelength range, SNV, SG-D2, detrend (5th order), centering and scaling in spectral pre-treatment showed R^2_{adj} value of 0.96 while RMSEC and RMSECV of 1.13 and 1.14 respectively. Again these parameters show that off-line NIR CI (line scan) PLS calibration models are not much impacted by additional spectral pre-treatments.

6.3.5 Comparison of NIRS and NIR CI (line scan) predictions inside feed frame

Owing to the complete spatial coverage of feed frame powders by NIR CI (line scan), it is possible to predict active concentrations over different sections of the feed frame; especially to compare similar powder region tested by both NIRS and NIR CI (line scan). Off-line NIR

CI (line scan) PLS models were used to predict the Ibuprofen and Ascorbic acid concentrations at middle section NIR CI (line scan) that resembled NIRS tested region inside the feed frame. The plot of the NIRS and NIR CI (line scan in the middle section) PLS model predicted concentrations of Ibuprofen (Fig 9a) and Ascorbic acid (Fig 9b) together with expected concentrations helped to visualize active concentration in respective section as well as the comparative accuracy of NIRS and NIR CI (line scan).

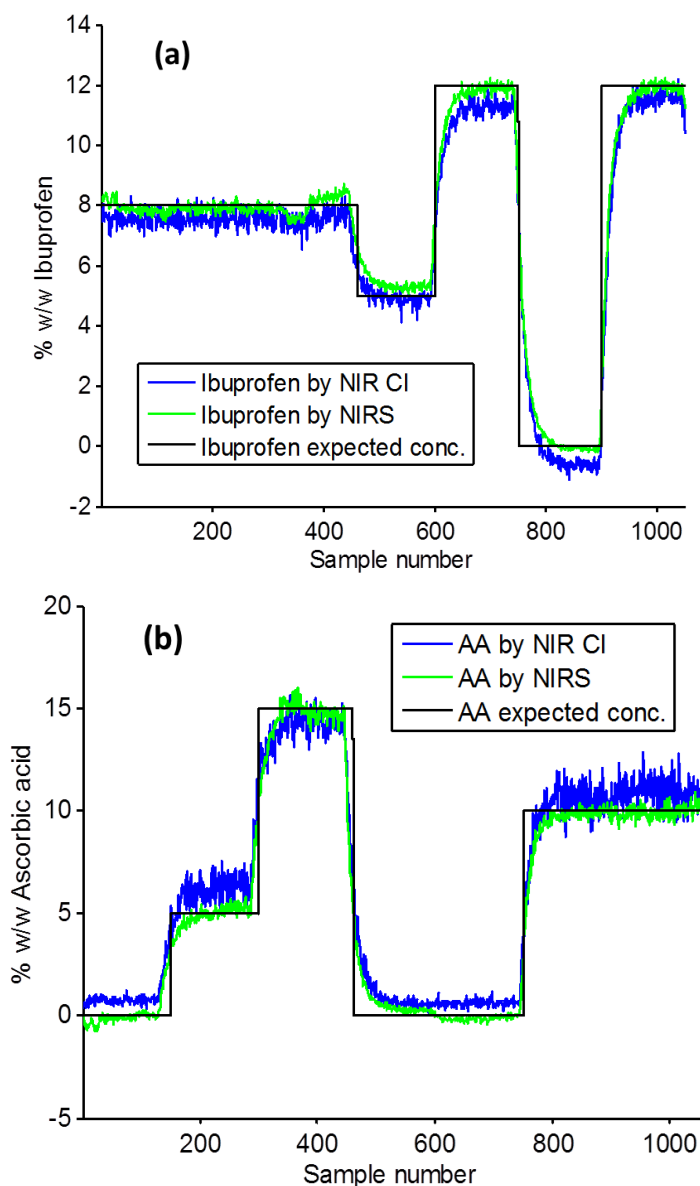


Figure 6.9: a) Plot of NIR CI (line scan) (in the middle section) and NIRS predicted concentrations for Ibuprofen b) Plot of NIR CI (line scan) (in middle sections) and NIRS predicted concentrations for Ascorbic acid

NIR CI (line scan) PLS model predicted concentrations of Ibuprofen and Ascorbic acid are compared between the methods as well as with the expected concentrations and the NIRS predicted concentrations to evaluate the closeness of the predicted concentrations with the expected concentrations as well as with the NIRS predicted concentrations.

Table 10 RMSE values for comparison between different image sections, NIRS predicted and expected concentrations inside the feed frame.

Table 6.3: RMSE for Ibuprofen concentration prediction (% w/w)

RMSE comparison between	Expected concentration (% w/w)	NIRS PLS predicted concentration (%w/w)
NIR CI (line scan) middle section	1.35	0.52
NIRS	1.20	0

Table 6.4: RMSE for Ascorbic acid concentration prediction (% w/w)

RMSE comparison between	Expected concentration (% w/w)	NIRS PLS predicted concentration (%w/w)
NIR CI (line scan) middle section	1.49	0.99
NIRS	1.24	0

As seen from the Figure 6.10a-b as well as RMSE values (table 6.4 and 6.4), Ibuprofen concentrations in middle section of the NIR CI (line scan) are close to NIRS predicted concentrations while both NIRS and NIR CI (line scan) predicted Ibuprofen concentrations are equally close to expected concentrations.

Comparatively, Ascorbic acid RMSE values are slightly higher than Ibuprofen concentrations but the middle section of the NIR CI (line scan) is still close to NIRS predicted concentrations and both NIRS and NIR CI (line scan) predicted Ascorbic acid concentrations are equally close to expected concentrations. This shows the comparability of NIR CI (line scan) and NIRS models for the feed frame monitoring.

6.4 Conclusion

Present work successfully shows that NIR CI (line scan) is capable for concentration monitoring in comparison to NIRS for more than one component in a complex pharmaceutical

composition. Off-line calibration models can be used to predict in-line concentrations using suitable spectral pre-treatments to remove baseline variations from the collected NIRS and NIR CI (line scan) data which are caused by experimental factors such as probe to powder distance, paddle wheel speed leading to density change, NIR light intensity variation as well as NIR illumination of powder samples. In addition to concentration prediction NIR CI (line scan) offers spectral data similar to NIRS covering entire powder sample along the horizontal direction. Considering the circular powder movement inside the feed frame, radial segregation of the powder is more prone to happen and may likely remain undetected by the NIRS which samples the powder just over a small area. NIR CI (line scan) data can be divided into several sections across the width of feed frame to probe the segregation.

CHAPTER 7 CONCLUSION

Pharmaceutical manufacturing is undergoing a phenomenal change in order to meet the regulatory expectations in terms of process understanding, monitoring, and control. Consequently, different PAT tools are being introduced in order to monitor the various manufacturing processes with the intent to increase process understanding and implementing process controls. In case of tablet manufacturing, feed frame monitoring during tablet compression has been much less studied than blending, granulation, milling, and drying which have been extensively studied and monitored. Although in the recent years NIRS PAT based feed frame monitoring has been initiated, to be a robust PAT tool, it needs further exploration owing to certain variables (e.g. location NIR of probe, paddle wheel speed, probe to powder distance, etc.) impacting NIRS performance for concentration predictions as reported in earlier studies. In addition there is a need for evaluating other potentially useful tools that may allow overcoming limitations of NIRS (e.g. smaller sample test area, lack of spatial information).

The present work concentrated on the introduction of NIR CI (area scan and line scan) as alternate PAT tool for feed frame monitoring while using NIRS as a reference method since it is already reported for this purpose. NIRS is studied to gain more understanding on its implementation for the feed frame monitoring a well subsequent tablet monitoring. Initial work aimed at evaluating the feasibility of NIR CI (area scan) using discrete wavelength band filters in a simple blend (comprising 3 components) as well as optimizing the sample presentation inside the feed frame. These off-line studies showed the usefulness of NIR CI (area scan) for concentration prediction in comparison to NIRS as well as to verify segregation potential of the powder blend inside the feed frame. Tested sample volume was seen 4 times than the NIRS although NIR probe in the present study is specially designed for feed frame monitoring with larger sample window (15×4 mm).

Following the successful feasibility of NIR CI (area scan), later studies concentrated on its evaluation to monitor in-line a pharmaceutically relevant complex blend comprising 1 active ingredient and 5 non-active ingredients. NIRS was used as reference inside feed frame and later to test compressed tablets in an in-line manner. Stratified tablet samples were also tested with off-line NIRS as well as UV assay to verify concentrations predicted inside the feed frame. Kinetics of concentration change inside feed frame and compressed tablets were compared to understand the implication of NIRS position as well as feed frame design in

concurrent concentration kinetics of feed frame and tablets. Results show that NIR CI (area scan) captures successfully all the concentration changes inside the feed frame but owing to multiple ingredients inside the blend the signal-to-noise ratio is slightly lower than NIRS. Due to the design of feed frame and NIR probe position, there was a delay in the onset of concentration change in the tablets from the moment it is first seen in feed frame. This information is very useful in continuous manufacturing where one can take preventive action well in advance to avoid mixing of uniform tablets with non-uniform tablets.

Later work aimed to further evaluate NIR CI (line scan) using spectrograph giving spectral information similar to NIRS while enhancing the spatial coverage of the tested sample in a multicomponent monitoring in a complex pharmaceutical blend. Results show that NIR CI (line scan) can successfully predict the concentration of 2 components simultaneously in comparison to NIRS as well as signal-to-noise ratio is higher as compared to NIR CI (area scan). With suitable pre-treatment, off-line calibration models can be transferred to in-line monitoring offering saving on the resources in the development of the calibration models. Middle section of NIR CI (line scan) shows very close results to NIRS; in addition, owing to larger sample coverage it offers an opportunity to test radial concentration profiles inside the feed frame to probe radial segregation if present inside the feed frame.

Overall, this Ph.D. project work successfully evaluates the feasibility of NIR CI for feed frame monitoring. In much simpler blends NIR CI (area scan) using single wavelength filter could be useful while for complex blends NIR CI (line scan) with spectrograph could be an alternate. In addition to increased sample size, NIR CI offers more potential to test adverse quality phenomenon such as segregation inside the feed frame. Methodologies and results obtained in this work could be definitely useful in the ongoing efforts of the pharmaceutical industry to understand, monitor and control the pharmaceutical manufacturing processes and to ensure quality by design in the manufactured products.

Conclusion en Français

La fabrication pharmaceutique est en pleine mutation pour répondre aux attentes réglementaires en termes de compréhension, de suivi et de contrôle des procédés. Par conséquent, différents outils PAT sont introduits afin de surveiller les différents procédés de fabrication dans le but d'accroître la compréhension des procédés et de mettre en œuvre des contrôles de procédé. Dans le cas de la fabrication de comprimés, les études sur la trémie

d'alimentation sont beaucoup moins nombreuses que pour la granulation, le broyage et le séchage. Au cours des dernières années, les études ont débuté sur le contrôle de la trémie d'alimentation par la NIRS PAT. Mais pour être un outil PAT robuste, elle doit être explorée davantage en fonction de certaines variables (par exemple position de la sonde NIR, vitesse de la roue, distance de la sonde au lit de poudre etc.) impactant les performances NIR pour les prédictions de concentration telles que rapportées dans des études antérieures. De plus, il y a le besoin d'étudier d'autres outils qui pourraient permettre de dépasser les limites de la NIRS (p. ex. zone d'analyse plus petite, manque d'informations spatiales).

Les travaux actuels se sont concentrés sur l'introduction de la NIR CI en tant qu'outil PAT alternatif pour le contrôle de la trémie d'alimentation tout en utilisant la NIRS comme méthode de référence puisqu'elle est déjà connue pour cette fin. La NIRS est étudiée pour mieux comprendre sa mise en œuvre dans la trémie d'alimentation suivi d'une surveillance ultérieure des comprimés. Les premiers travaux visaient à évaluer la faisabilité de la NIR CI en utilisant des filtres à bande de longueur d'onde discrète dans un mélange simple (comportant 3 composants) ainsi qu'à optimiser la présentation de l'échantillon dans la trémie d'alimentation. Ces études hors ligne ont montré l'utilité de la NIR CI pour la prédiction de concentration par rapport à la NIRS, ainsi que pour vérifier le potentiel de ségrégation du mélange de poudres dans la trémie d'alimentation. Le volume d'échantillon testé se trouve être 4 fois plus grand que celui de la NIRS, bien que la sonde NIR dans la présente étude soit spécialement conçue pour le contrôle de la trémie d'alimentation avec une fenêtre d'échantillon plus grande (15 x 4 mm).

Suite à la faisabilité réussie de la NIR CI en format filtre unique, les études suivantes se sont concentrées sur son évaluation pour surveiller en ligne un mélange pharmaceutique complexe et approprié, comportant 1 ingrédient actif et 5 ingrédients non-actifs. La NIRS a été utilisée comme analyse de référence à l'intérieur de la trémie d'alimentation et plus tard pour tester les comprimés en ligne. Des échantillons de comprimés stratifiés sont également testés avec la NIRS hors ligne ainsi qu'en UV pour vérifier les concentrations prédites à l'intérieur de la trémie d'alimentation. La cinétique du changement de concentration à l'intérieur de la trémie d'alimentation et des comprimés a été comparée pour comprendre l'implication de la position de la NIRS ainsi que la conception de la trémie d'alimentation dans la cinétique de la concentration des comprimés. Les résultats montrent que la NIR CI capture

avec succès tous les changements de concentration à l'intérieur de la trémie d'alimentation, mais en raison de plusieurs ingrédients à l'intérieur du mélange, le rapport signal / bruit est légèrement inférieur à celui de la NIRS. En raison de la conception de la trémie d'alimentation et de la position de la sonde NIR, il y a eu un retard dans le changement de concentration dans les comprimés à partir du moment où il a été vu pour la première fois dans le cadre d'alimentation. Cette information est très utile dans la fabrication en continu où l'on peut prendre des mesures préventives bien à l'avance pour éviter le mélange de comprimés uniformes avec des comprimés non uniformes.

Les travaux ultérieurs visaient à évaluer davantage la NIR CI en utilisant un spectrographe donnant des informations spectrales similaires à celles de la NIRS tout en améliorant la couverture spatiale de l'échantillon testé dans une surveillance multicomposant dans un mélange pharmaceutique complexe. Les résultats montrent que la NIR CI peut prédire avec succès la concentration de 2 composants simultanément ce qui n'est pas le cas de la spectroscopie NIRS, et que le rapport signal sur bruit est plus élevé que la NIR CI à filtre unique. Avec un pré-traitement approprié, les modèles d'étalonnage hors ligne peuvent être transférés à la surveillance en ligne, ce qui permet d'économiser sur les ressources dans le développement des modèles d'étalonnage. La section centrale de la NIR CI montre des résultats très proches de la NIRS; En outre, grâce à une plus grande couverture des échantillons, il est possible de tester les profils de concentration radiale à l'intérieur de la trémie d'alimentation afin de sonder la ségrégation radiale si elle est présente à l'intérieur de celle-ci.

Dans l'ensemble, ce travail de thèse a permis d'évaluer avec succès la faisabilité de la NIR CI pour la surveillance de l'alimentation. Dans des mélanges beaucoup plus simples, la NIR CI en format de filtre unique pourrait être utile tandis que pour les mélanges complexes, la NIR CI avec spectrographe pourrait être une alternative. En plus de l'augmentation de la taille de l'échantillon, la NIR CI offre plus de potentiel pour tester les phénomènes de qualité défavorable tels que la ségrégation à l'intérieur de la trémie d'alimentation. Les méthodologies et les résultats obtenus dans ce travail pourraient être certainement utiles dans les efforts continus de l'industrie pharmaceutique pour comprendre, contrôler et maîtriser les procédés de fabrication pharmaceutiques et pour assurer la qualité par la conception dans les produits manufacturés.

CHAPTER 8 FUTURE PLAN

Present work successfully demonstrates the feasibility of NIR CI in dynamic process environment during the pharmaceutical tablet manufacturing. Depending upon the expected level of scrutiny NIR CI can be implemented in area scan or line scan format. Considering present Ph.D. work as a proof of concept for NIR CI based in-line PAT applications, pharmaceutical industry can adopt the experimental and analytical methodologies presented in this work for monitoring the other manufacturing operations. Future work can be divided in 2 areas: first for further consolidating NIR CI application in the feed frame monitoring and second for evaluating NIR CI for its potential use in other dynamic process monitoring applications.

Consolidation of NIR CI based feed frame PAT should concentrate on further ameliorating experimental set up for longer duration process monitoring during the commercial production batches considering factors such as cooling of NIR camera, fixing the NIR light, wireless data transfer, sample area variations, and PAT method validation for regulatory filing.

Further evaluation of NIR CI for pharmaceutical process monitoring can involve the other processes during tablet manufacturing (e.g. monitoring of the granulation, compressed tablets, etc.) or monitoring the manufacturing processes of other dosage forms such as liquids, semisolids.

ANNEXES

A.1 NIRS technology

The MicroNIR spectrometer from VIAVI is a particular example of such small and handy spectrophotometers which have a versatile application potential. Weighing less than 60 g and measuring less than 50 mm in diameter, it is more practical to cost-effectively implement as an on-line and at-line tool for process development, process transfer, and manufacturing process monitoring and control.



Figure A.8.1: MicroNIR in SS housing

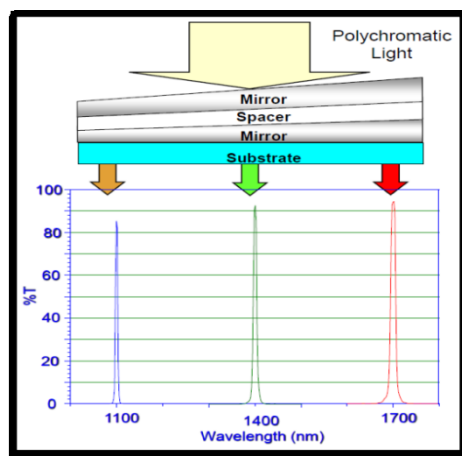


Figure A.8.2: Working principle of the linear variable filter (LVF)

The MicroNIR uses a linear variable filter (LVF) component mounted over a diode array detector that separates incoming light into individual wavelengths. The working principle of the LVF is provided in Figure 3. The spectrometer integrates the light source and readout electronics inside a small construction. It can be mounted directly on the window of a blender, a fluid bed dryer, or any other process without the need for costly fiber optic probes. It can also operate in a wireless configuration, allowing use on rotating blenders for end-point monitoring [135].

LVF is mounted directly over a linear detector array with multiple pixel elements. Light illuminates the LVF & the wavelength transmitted through the filter is dependent on its linear position along the filter. Each pixel element of the linear array will detect a specific wavelength [136].

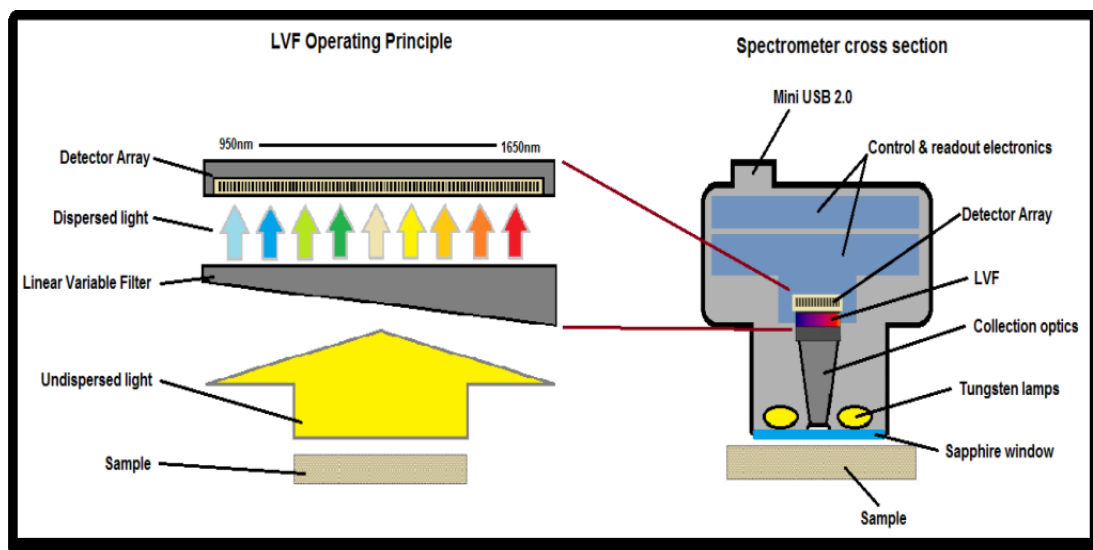


Figure A.8.3: Schematic representations of LVF principle

LVF in MicroNIR is used as the dispersive element versus traditional diffraction based spectrometers. The LVF is a dielectric thin-film Fabry-Perot bandpass filter deposited using energetic processes, well-known to produce stable and reliable optical components. The LVF filter coating used in the MicroNIR is intentionally wedged in one direction. Since the center wavelength of the bandpass filter is a function of the coating thickness, the peak transmitted wavelength varies continuously along the direction of the wedge [137].

Table A.9: Properties of Micro NIR spectrophotometer

Weight	60 grams
Dimensions	45mm diameter x 42mm height
Spectral Range Micro NIR 1700:	950 -1650nm
Number of pixels	128 pixels, 125 points standardized grid
Optical Resolution	<1.25 % of center wavelength, i.e. at 1000nm wavelength, resolution is <12.5nm
Geometric Resolution	6.25nm per pixel
Wavelength Accuracy	< 3 nm, as compared to NIST SRM-2036
Wavelength Repeatability	< 1 nm, as compared to NIST SRM-2036
Power Requirement	USB powered, <500mA at 5V

A.2 SPECTROGRAPH – NIR CI

Spectrometers or spectrophotometers are usually able to measure optical spectrum from a surface area as one point. This is done either with one detector scanning the spectrum in narrow wavelength bands or with an array detector, in which case all the spectral components are acquired at once. If one desires to measure the spectrum at several spatial locations of a surface, the target under examination or the measuring instrument has to be mechanically scanned. Technically it is not possible to simultaneously measure spectral information across a 2 -dimensional surface matrix, because this would lead to a four-dimensional information space (X, Y -coordinates, wavelength, and intensity). This is obviously impossible to realize with standard two-dimensional detectors which can register only position and intensity of radiation at a time. This leads to the idea of measuring the spatial information across a line only (X-axis with a specified length and small but finite width) and the spectral information (wavelength and intensity) for each point (pixel) in this line (Fig. A.2.1.).

A 3-dimensional information space results that can be measured with an area (matrix) detector array connected to a dispersive, stationary spectrograph module. One dimension of the detector now constitutes a spatial line image and the other dimension measures the spectrum for each line pixel. This is the operating principle of the imaging spectrograph. A NIR camera equipped with an imaging spectrometer instrument is capable of simultaneously measuring the optical spectrum components and the spatial location of the powder surface. In present work spectrograph designed for 900 - 1700nm wavelength range is used to transform a NIR camera into a line-scan spectral imaging device.

NIR CI was measured in 256×320 pixel format where 256 pixels represented spectral axis while 320 pixels represented spatial axis. NIR CI taken inside feed frame represented $20 \text{ mm} \times 36 \text{ mm}$ actual feed frame powder area. 20 mm along the powder movement direction while 36 mm along the width of feed frame. All image pixels were averaged in spatial dimension since powder was in continuous motion and we are interested in radial segregation rather than segregation in the direction of the powder movement. The resulting output for each NIR CI was a NIR spectrum over 900-1700 nm (Fig. A.2.1.).

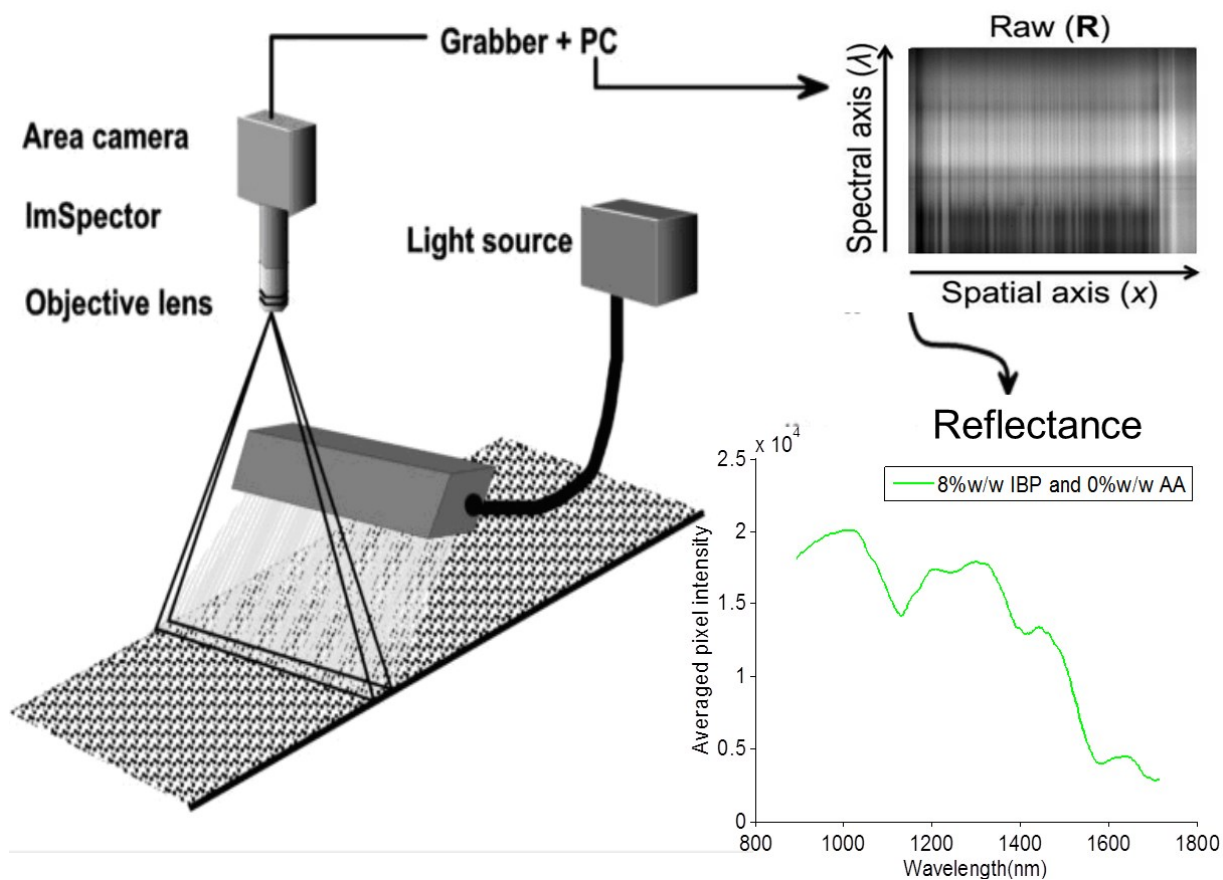


Figure A.8.4: Schematic representations of NIR CI scanning and output

Figure A.2.2 and A.2.3 shows side and front view of the spectrograph used in this work.



Figure A.8.5: Spectrograph side view

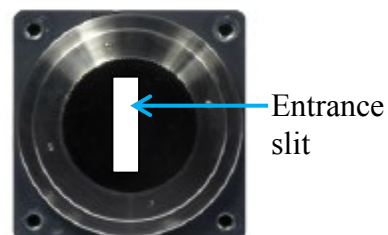


Figure A.8.6: Spectrograph front view (slit is enlarged for visibility)

A.3 NIRS SPECTAL PRE-TREATMENTS

All of the NIRS measurements performed inside the feed frame and the tablets are performed in-line manner causing certain variations in the spectra due to sample presentation (section 1.3.2). These variations were mostly due to physical parameters such as density change, particle size variation, particle shape (inside the feed frame) while hardness variation (in case of tablets) as well as probable variation in NIR source intensity over time. The contribution of these factors to the recorded NIR spectra is purely non-essential for the present purpose of data analysis since concentration monitoring is our main target. Consequently, these artifacts were removed from the NIR spectral data using different mathematical pre-treatments to enhance spectral features [138] as described below.

a) *Standard normal variate (SNV)*

Standard normal variate (SNV) is a widely known method to reduce spectral distortions due to NIR light scattering. SNV centers and scales each spectrum individually, so each has a mean equal to 0 and standard deviation equal to 1. SNV removes slope variation from each wavelength on an individual basis [139] thus all samples have an equal impact on the model. The standard deviation of all of the pooled variables is calculated for a given sample and entire sample is normalized using this standard deviation. At the same time, individual spectrum mean value is subtracted from each individual value of the spectrum as shown below.

$$\bar{x} = \frac{\sum_{j=1}^n x_{i,j}}{n} \quad (\text{A.3.1})$$

$$w_i = \sqrt{\frac{\sum_{j=1}^n (x_{i,j} - \bar{x})^2}{(n-1)}} + \delta^{-1} \quad (\text{A.3.2})$$

n is the number of variables, $x_{i,j}$ is value of the j^{th} variable in the i^{th} sample, δ is user definable offset which is meant to avoid over normalization of sample having close to zero standard deviation. Default value of the δ is zero [33] .

b) *Savitzky-Golay smoothing and derivatives*

Smoothing is a low-pass filter used for removing high-frequency noise from the samples. In case of NIR spectra, this operation is done separately on each row of the data

matrix and acts on adjacent variables. Smoothing assumes that variables which are near to each other in the data matrix (i.e., adjacent columns) are related to each other and contain similar information which can be averaged together to reduce noise without a significant loss of the signal of interest. Savitzky-Golay smoothing fits polynomials of different orders over the selected range of variables, which is called as filter size.

Derivatives de-emphasize lower frequencies and emphasize higher frequencies thus they tend to accentuate noise (high-frequency signal). For this reason, the Savitzky-Golay smoothing is used simultaneously as derivative is taken which helps in improving the utility of derivatized data. In case of the first derivative, each variable in a sample is subtracted from its immediate neighboring variable. This subtraction removes the signal which is the same between the two variables and leaves only the part of the signal which is different. When performed on an entire sample, a first derivative effectively removes any offset from the sample and de-emphasizes lower-frequency signals. A second derivative is calculated by repeating the sampling process, which further accentuates higher-frequency features [33].

c) Detrend

Detrend is useful when constant, linear or curved offset present in the spectral data. Detrend fits a polynomial of a given order to the entire sample and removes/subtracts this polynomial from the sample data. Considering the fact that detrend fits the polynomial to all points of the spectra including baseline as well as signal, it only works well when largest contributor to sample spectra is the background interference. On the contrary, if the significant contribution to the spectra is from the sample itself then detrend tends to remove useful information from the spectra, which obviously not desirable.

d) Multiple scatter correction (MSC)

MSC helps to remove scaling and offset effects from the spectral data. MSC corrects the spectra by regressing measured spectrum against a reference spectrum and then correcting measured spectrum using slope and intercept of regression fit. The reference spectrum is generally the mean spectrum. It defines X as column vector corresponding to the raw spectrum (i.e. spectrum to be corrected), r as vector corresponding to reference spectrum. These vectors are often mean centered using the mean of the respective spectrum as

$$X_c = x_i - \bar{x} \quad (\text{A.3.3})$$

X_c is mean centered raw spectrum, \bar{x} is mean of raw spectra and x_i is value of the i^{th} wavelength in sample spectrum.

$$r_c = r_{i,j} - \bar{r} \quad (\text{A.3.4})$$

r_c is mean centered reference spectrum, \bar{r} is mean of reference spectrum and r_i is value of the i^{th} wavelength in reference the spectrum.

The multiplicative factor (b) is found as:

$$r_c = bX_c \quad (\text{A.3.5})$$

$$b = (r_c^T r_c)^{-1} r_c^T X_c \quad (\text{A.3.6})$$

The corrected spectrum \hat{X} is given by;

$$\hat{X} = X_c/b + \bar{r} \quad (\text{A.3.7})$$

e) Centering and scaling to unit variance

Centering and scaling to unit variance also called as ‘autoscale’ is a column-wise pre-treatment which makes the spectral data ready for multivariate model analysis. The mathematical treatment involves subtracting column mean and then dividing each column (variable) by the standard deviation of the column, consequently each column in the resulting data matrix has mean of zero and standard deviation of one

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